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=> d his

     (FILE 'HOME' ENTERED AT 11:11:06 ON 06 JUN 2006)

     FILE 'CAPLUS, MEDLINE' ENTERED AT 11:11:17 ON 06 JUN 2006
L1             7 S INFLAMMATION (P) CADPR
L2            22 S INFLAMMAT? (P) CADPR
L3             1 S ENDOTOXEMIA? (P) CADPR
L4            12 S ASTHMA? (P) CADPR
L5             1 S SEPSIS? (P) CADPR
L6             1 S HEMORR? (P) CADPR
L7             1 S SHOCK? (P) CADPR
L8             1 S PANCREATITIS (P) CADPR
L9             1 S CROHN? (P) CADPR
L10            1 S ULCER? (P) CADPR
L11          102 S ADP (P) PHOSPHOROTHIOATE
L12            0 S CADPR (P) PHOSPHOROTHIOATE
L13            0 S CADP (P) PHOSPHOROTHIOATE
L14            0 S CADPR (P) PHOSPHOROTHIOATE
L15            0 S CADPR (P) PHOSPHOROAMIDATE
L16          149 S CADPR (P) ANALOG?
L17            4 S CADPR (P) ANALOG? (P) DISEASE?
L18           16 S CADPR (P) ANALOG? (P) CONDITION?
L19           18 S CADPR (P) PATIENT?
L20            4 S CADPR (P) ADMINISTER?
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L2 ANSWER 11 OF 22 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:415458 CAPLUS
DOCUMENT NUMBER: 127:134649
TITLE: Role of cyclic ADP-ribose in ATP-activated potassium currents in alveolar macrophages
AUTHOR(S): Ebihara, Satoru; Sasaki, Tsukasa; Hida, Wataru; Kikuchi, Yoshihiro; Oshiro, Takako; Shimura, Sanae; Takasawa, Shin; Okamoto, Hiroshi; Nishiyama, Akinori; Akaike, Norio; Shirato, Kunio
CORPORATE SOURCE: First Department of Internal Medicine, the Department of Biochemistry, and the First Department of Physiology, Tohoku University School of Medicine, Sendai, 980-77, Japan
SOURCE: Journal of Biological Chemistry (1997), 272(25), 16023-16029
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB There is growing evidence that extracellular ATP causes a dramatic change in the membrane conductance of a variety of **inflammatory** cells. In the present study, using the nystatin perforated patch recording configuration, the authors found that ATP (0.3-30 μM) induced a transient outward current in a concentration-dependent manner and that the reversal potential of the ATP-induced outward current was close to the K+ equilibrium potential, indicating that the membrane behaves like a K+ electrode in the presence of ATP. The first application of ATP to alveolar macrophages perfused with Ca2+-free external solution could induce the outward current, but the response to ATP was diminished with successive applications. Intracellular perfusion with a Ca2+ chelator, BAPTA, also diminished the response. When cyclic ADP-ribose (**cADPR**) was applied to the macrophage cytoplasm, a transient outward current was elicited. Thereafter, the successive outward current was inhibited, suggesting the involvement of **cADPR** in the response. Intracellular perfusion with inositol 1,4,5-trisphosphate also induced a transient outward current, but the successive current was not inhibited. The ATP-induced outward current was abolished when 8-amino-**cADPR** (as a blocker of **cADPR**, 10-6-10-5 M) was introduced into the cytoplasm. Homogenates of alveolar macrophages showed both ADP-ribosyl cyclase and **cADPR** hydrolase activities, and CD38 (ADP-ribosyl cyclase/**cADPR** hydrolase) expression was confirmed by reverse transcriptase-polymerase chain reaction and Western blot analyses. These results indicate that ATP activates K+ currents by releasing Ca2+ from **cADPR**-sensitive internal Ca2+ stores.

L2 ANSWER 12 OF 22 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:820276 CAPLUS
TITLE: The whoosh and trickle of calcium signalling
AUTHOR(S): Murphy, C. T.; Poll, C. T.; Westwick, J.
CORPORATE SOURCE: School Pharmacy Pharmacology, University Bath, Bath, UK
SOURCE: Cell Calcium (1995), 18(3), 245-51
CODEN: CECADV; ISSN: 0143-4160
PUBLISHER: Churchill Livingstone
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The importance of phospholipase C catalyzed hydrolysis of phosphatidylinositol-(4,5)bisphosphate (PtdIns(4,5)P2) to inositol-(1,4,5)trisphosphate (Ins(1,4,5)P3) and sn-1,2-diacylglycerol in the signal transduction pathways of eukaryote cells, in response to extracellular stimuli, is now widely recognized. Although nearly 60 naturally occurring inositol phosphates have been identified in mammalian

cells, mobilization of Ca2+ from the intracellular stores has been most commonly attributed to the generation of Ins(1,4,5)P3 [1]. However, there is increasing evidence for the presence of ryanodine receptors (RyR) in non-excitable cells and for cADP-ribose (**cADPr**) as the signalling mol. responsible for Ca2+ release via the RyR. But what is the purpose for the co-existence of these two intracellular Ca2+ channels in non-excitable cells and why are they so heterogeneous in their distribution these questions were explored at the recent International Symposium Calcium Signalling in **Inflammatory** Cells. Depletion of the intracellular Ca2+ pools is followed by entry of Ca2+ into the cell across the plasma membrane, but he mechanism(s) underlying this 'capacitative Ca2+ entry' is not well understood. Many potential signalling pathways which may account for capacitative Ca2+ entry have been proposed although none have been unanimously accepted. New developments in the elucidation of the mechanism responsible for capacitative Ca2+ entry and how Ca2+ entry is regulated, together with progress in the characterization of plasma membrane Ca2+ entry channels were also discussed at this symposium.

L2 ANSWER 13 OF 22 MEDLINE on STN
ACCESSION NUMBER: 2006272844 IN-PROCESS
DOCUMENT NUMBER: PubMed ID: 16547971
TITLE: CCL5 evokes calcium signals in microglia through a kinase-, phosphoinositide-, and nucleotide-dependent mechanism.
AUTHOR: Shideman C R; Hu S; Peterson P K; Thayer S A
CORPORATE SOURCE: Department of Pharmacology, University of Minnesota, Minneapolis, Minnesota.
SOURCE: Journal of neuroscience research, (2006 Jun 1) Vol. 83, No. 8, pp. 1471-84.
Journal code: 7600111. ISSN: 0360-4012.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: NONMEDLINE; IN-DATA-REVIEW; IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 17 May 2006
Last Updated on STN: 17 May 2006

AB Microglia, the resident macrophages of the CNS, are responsible for the innate immune response in the brain and participate in the pathogenesis of certain neurodegenerative disorders. Chemokines initiate activation and migration of microglia. The beta-chemokine CCL5 induces an elevation in intracellular calcium concentration ([Ca(2+)](i)) in human microglia. Here, we examined the signal transduction pathway linking activation of chemokine receptor CCR5 to an elevation in [Ca(2+)](i) in cultured microglia by using pharmacological approaches in combination with Fura-2-based digital imaging. The CCL5-induced response required Janus kinase (Jak) activity and the stimulation of an inhibitory G protein. Multiple downstream signaling pathways were involved, including phosphatidylinositol 3-kinase (PI3K), Bruton's tyrosine kinase (Btk), and phospholipase C (PLC)-mediated release of Ca(2+) from inositol 1,4,5-trisphosphate (IP(3))-sensitive stores. Activation of both the kinase and the lipase pathways was required for eliciting the Ca(2+) response. However, the majority of the [Ca(2+)](i) increase was derived from sources activated by NAD metabolites. Cyclic ADP-ribose (**cADPR**) evoked Ca(2+) release from intracellular stores, and ADPR evoked Ca(2+) influx via a nimodipine-sensitive channel. Thus, a multistep cascade couples CCR5 activation to Ca(2+) increases in human microglia. Because changes in [Ca(2+)](i) affect chemotaxis, secretion, and gene expression, pharmacologic modulation of this pathway may alter **inflammatory** and degenerative processes in the CNS. (c) 2006 Wiley-Liss, Inc.

L2 ANSWER 14 OF 22 MEDLINE on STN
ACCESSION NUMBER: 2005523230 MEDLINE

DOCUMENT NUMBER: PubMed ID: 16168959
TITLE: Non-specific effects of 4-chloro-m-cresol may cause calcium flux and respiratory burst in human neutrophils.
AUTHOR: Hauser Carl J; Kannan Kolenkode B; Deitch Edwin A; Itagaki Kiyoshi
CORPORATE SOURCE: The Department of Surgery, Division of Trauma, UMDNJ-New Jersey Medical School, Newark, 07103, USA.
SOURCE: Biochemical and biophysical research communications, (2005 Nov 4) Vol. 336, No. 4, pp. 1087-95.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200512
ENTRY DATE: Entered STN: 4 Oct 2005
Last Updated on STN: 18 Dec 2005
Entered Medline: 12 Dec 2005

AB We examined the effects of 4-chloro-m-cresol (4-CmC, a potent and specific activator of ryanodine receptors) on Ca(2+)-release/influx and respiratory burst in freshly isolated human PMN as well as HL60 cells. 4-CmC induces Ca(2+) store-depletion in a dose-dependent manner at concentrations between 400muM and 3mM, however no dose-dependent effect on Ca(2+)-influx was found. 4-CmC depleted Ca(2+) stores that were shared with the GPC agonists such as fMLP and PAF, and therefore 4-CmC presumably depletes Ca(2+) from ER. Since the authentic ligand for RyR is cyclic ADP-ribose (**cADPR**), we assessed the functional relevance of RyR in PMN by studying the presence and function of membrane-bound ADP-ribosyl cyclase (CD38) in PMN. First, expression of CD38 was confirmed by RT-PCR using cDNA from HL60 cells. Second, PMN from trauma patients showed significantly enhanced CD38 expression than those from healthy volunteers. In addition, although no chemotaxis effect was detected by 4-CmC, it stimulated respiratory burst in PMN in a dose-dependent manner. Our findings suggest that RyRs exist in human PMN and that RyR pathway may play an active role in **inflammatory** PMN calcium signaling. 8-Br-**cADPR** and cyclic 3-deaza-ADP did not have inhibitory effects either on 4-CmC-induced Ca(2+) store-depletion or on respiratory burst, on the other hand, PLC inhibitor, U73122, completely attenuated both 4-CmC-induced Ca(2+) store-depletion and respiratory burst. Although it has been used as a specific activator of RyR, 4-CmC has non-specific effects which cause Ca(2+) store-depletion and respiratory burst at least in human PMN.

L2 ANSWER 15 OF 22 MEDLINE on STN
ACCESSION NUMBER: 2004383527 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15266023
TITLE: Tumor necrosis factor-alpha differentially regulates the expression of proinflammatory genes in human airway smooth muscle cells by activation of interferon-beta-dependent CD38 pathway.
AUTHOR: Tliba Omar; Panettieri Reynold A Jr; Tliba Samira; Walseth Timothy F; Amrani Yassine
CORPORATE SOURCE: Pulmonary, Allergy, and Critical Care Division, Department of Medicine, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania 19104-6160, USA.
CONTRACT NUMBER: 2R01-HL55301 (NHLBI)
DA11806 (NIDA)
HL67663 (NHLBI)
SOURCE: Molecular pharmacology, (2004 Aug) Vol. 66, No. 2, pp. 322-9.
Journal code: 0035623. ISSN: 0026-895X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 200408
ENTRY DATE: Entered STN: 4 Aug 2004
Last Updated on STN: 31 Aug 2004
Entered Medline: 30 Aug 2004

AB Recent evidence suggests that CD38, an ectoenzyme that converts NAD(+) to cyclic ADP-ribose (**cADPr**), may play a role in cytokine-induced airway smooth muscle (ASM) cell hyper-responsiveness, a key feature associated with chronic asthma. In the present study, we investigated the major signaling pathways by which tumor necrosis factor-alpha (TNFalpha) induces CD38 expression and its role in regulating gene expression in human ASM cells. Using flow cytometry analyses, TNFalpha enhanced CD38 expression in a manner that was time-(0-24 h), concentration-(0.1-40 ng/ml), and protein synthesis-(cycloheximide blockade) dependent. A selective agonistic antibody against tumor necrosis factor receptor (TNFR) 1 also augmented CD38 expression, whereas anti-TNFR2 antagonistic antibody did not prevent the TNFalpha response. Inhibition of the Janus activated kinase/signal transducer and activator of transcription pathways using the soluble inhibitor 2-(1,1-dimethylethyl)-9-fluoro-3,6-dihydro-7H-benz-[h]imidaz[4,5-f]isoquinolin-7-one (DBI) or with neutralizing antibody against interferon beta (IFNbeta) completely abrogated TNFalpha-induced CD38 expression at both protein and mRNA levels. Combining TNFalpha (0.1 and 1 ng/ml) and IFNbeta (100 IU/ml) at concentrations alone that had little effect on CD38 expression induced a robust synergistic induction of CD38 mRNA and protein levels. 8-Bromo-**cADPr**, a **cADPr** antagonist, significantly augmented TNFalpha-induced interleukin-6 secretion, whereas regulated on activation normal T cell expressed and secreted secretion was suppressed. 8-Bromo-**cADPr**, however, did not affect TNFalpha-induced cell surface expression of intercellular adhesion molecule-1. Our study is the first to demonstrate that IFNbeta-dependent activation of CD38 pathway is a novel component by which TNFalpha differentially regulates the expression of **inflammatory** genes in ASM cells.

L2 ANSWER 16 OF 22 MEDLINE on STN
ACCESSION NUMBER: 2004138075 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15030772
TITLE: Regulation of dendritic cell trafficking by the ADP-ribosyl cyclase CD38: impact on the development of humoral immunity.
AUTHOR: Partida-Sanchez Santiago; Goodrich Stephen; Kusser Kim; Oppenheimer Norman; Randall Troy D; Lund Frances E
CORPORATE SOURCE: Trudeau Institute, 154 Algonquin Avenue, Saranac Lake, NY 12983, USA.
CONTRACT NUMBER: R01-AI43589 (NIAID)
R01-AI43629 (NIAID)
SOURCE: Immunity, (2004 Mar) Vol. 20, No. 3, pp. 279-91.
Journal code: 9432918. ISSN: 1074-7613.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200404
ENTRY DATE: Entered STN: 20 Mar 2004
Last Updated on STN: 14 Apr 2004
Entered Medline: 13 Apr 2004

AB Mice lacking CD38, an ectoenzyme that generates the calcium-mobilizing metabolite **cADPR**, make reduced T cell-dependent antibody responses. Despite the predicted role for CD38 in B cell activation, we find that CD38 regulates the migration of dendritic cell (DC) precursors from the blood to peripheral sites and controls the migration of mature DCs from sites of **inflammation** to lymph nodes. Thus, T cells are inefficiently primed in Cd38(-/-) mice, leading to poor humoral immune responses. We also show that CD38 and **cADPR** modulate calcium

mobilization in chemokine-stimulated DCs and are required for the chemotaxis of immature and mature DCs to CCL2, CCL19, CCL21, and CXCL12. Therefore, CD38 regulates adaptive immunity by controlling chemokine receptor signaling in DCs.

L2 ANSWER 17 OF 22 MEDLINE on STN
ACCESSION NUMBER: 2004047399 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14734775
TITLE: Chemotaxis and calcium responses of phagocytes to formyl peptide receptor ligands is differentially regulated by cyclic ADP ribose.
AUTHOR: Partida-Sanchez Santiago; Iribarren Pablo; Moreno-Garcia Miguel E; Gao Ji-Liang; Murphy Philip M; Oppenheimer Norman; Wang Ji Ming; Lund Frances E
CORPORATE SOURCE: Trudeau Institute, Saranac Lake, NY 12983, USA.
SOURCE: Journal of immunology (Baltimore, Md. : 1950), (2004 Feb 1) Vol. 172, No. 3, pp. 1896-906.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200405
ENTRY DATE: Entered STN: 30 Jan 2004
Last Updated on STN: 10 May 2004
Entered Medline: 7 May 2004

AB Cyclic ADP ribose (**cADPR**) is a calcium-mobilizing metabolite that regulates intracellular calcium release and extracellular calcium influx. Although the role of **cADPR** in modulating calcium mobilization has been extensively examined, its potential role in regulating immunologic responses is less well understood. We previously reported that **cADPR**, produced by the ADP-ribosyl cyclase, CD38, controls calcium influx and chemotaxis of murine neutrophils responding to fMLF, a peptide agonist for two chemoattractant receptor subtypes, formyl peptide receptor and formyl peptide receptor-like 1. In this study, we examine whether **cADPR** is required for chemotaxis of human monocytes and neutrophils to a diverse array of chemoattractants. We found that a **cADPR** antagonist and a CD38 substrate analogue inhibited the chemotaxis of human phagocytic cells to a number of formyl peptide receptor-like 1-specific ligands but had no effect on the chemotactic response of these cells to ligands selective for formyl peptide receptor. In addition, we show that the **cADPR** antagonist blocks the chemotaxis of human monocytes to CXCR4, CCR1, and CCR5 ligands. In all cases, we found that **cADPR** modulates intracellular free calcium levels in cells activated by chemokines that induce extracellular calcium influx in the apparent absence of significant intracellular calcium release. Thus, **cADPR** regulates calcium signaling of a discrete subset of chemoattractant receptors expressed by human leukocytes. Since many of the chemoattractant receptors regulated by **cADPR** bind to ligands that are associated with clinical pathology, **cADPR** and CD38 represent novel drug targets with potential application in chronic **inflammatory** and neurodegenerative disease.

L2 ANSWER 18 OF 22 MEDLINE on STN
ACCESSION NUMBER: 2003118202 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12514117
TITLE: CD38/cyclic ADP-ribose-mediated Ca2+ signaling contributes to airway smooth muscle hyper-responsiveness.
AUTHOR: Deshpande Deepak A; Walseth Timothy F; Panettieri Reynold A; Kannan Mathur S
CORPORATE SOURCE: Department of Veterinary PathoBiology, University of Minnesota, St. Paul, Minnesota 55108, USA.
SOURCE: The FASEB journal : official publication of the Federation

of American Societies for Experimental Biology, (2003 Mar) Vol. 17, No. 3, pp. 452-4. Electronic Publication: 2003-01-02.
Journal code: 8804484. E-ISSN: 1530-6860.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200304
ENTRY DATE: Entered STN: 13 Mar 2003
Last Updated on STN: 2 Apr 2003
Entered Medline: 1 Apr 2003

AB We previously demonstrated that cyclic ADP-ribose (**cADPR**) elicits Ca2+ release in airway smooth muscle (ASM) cells through ryanodine receptor channels. CD38 is a cell surface protein that catalyzes the synthesis and degradation of **cADPR**. In **inflammatory** diseases such as asthma, augmented Ca2+ responses and Ca2+ sensitivity contribute to increased ASM contractility in response to agonists. In this study, we investigated the regulation of CD38 expression and the role of **cADPR**-mediated Ca2+ release in airway **inflammation**. Human ASM cells in culture between the second and fifth passages were exposed to tumor necrosis factor alpha (TNF-alpha), interleukin 1beta, or interferon gamma, or bovine serum albumin (controls). CD38 expression was measured by reverse transcriptase-polymerase chain reaction (RT-PCR), real-time PCR, and Western blot analysis, and ADP-ribosyl cyclase activity was assayed with nicotinamide guanine dinucleotide as the substrate. Ca2+ responses to acetylcholine, bradykinin, and thrombin were measured in fura-2AM-loaded cells by fluorescence microscopy. Cytokines caused significant augmentation of CD38 expression, ADP-ribosyl cyclase activity, and Ca2+ responses to the agonists, compared with the control. TNF-alpha effects were greater than those of the other two cytokines. The **cADPR** antagonist 8-bromo-**cADPR** attenuated the Ca2+ responses to the agonists in control and cytokine-treated cells, with the magnitude of inhibition correlating with the level of CD38. This study provides the first demonstration of a role for CD38-**cADPR** signaling in a model of **inflammatory** airway disease.

L2 ANSWER 19 OF 22 MEDLINE on STN
ACCESSION NUMBER: 2000422562 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10922045
TITLE: Nitric oxide and salicylic acid signaling in plant defense.
AUTHOR: Klessig D F; Durner J; Noad R; Navarre D A; Wendehenne D; Kumar D; Zhou J M; Shah J; Zhang S; Kachroo P; Trifa Y; Pontier D; Lam E; Silva H
CORPORATE SOURCE: Waksman Institute and Department of Molecular Biology and Biochemistry, Rutgers, The State University of New Jersey, 190 Frelinghuysen Road, Piscataway, NJ 08854-8020, USA.. klessig@mcbl.rutgers.edu
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (2000 Aug 1) Vol. 97, No. 16, pp. 8849-55. Ref: 75
Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Space Life Sciences
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 15 Sep 2000
Last Updated on STN: 15 Sep 2000
Entered Medline: 5 Sep 2000

AB Salicylic acid (SA) plays a critical signaling role in the activation of plant defense responses after pathogen attack. We have identified several potential components of the SA signaling pathway, including (i) the

H(2)O(2)-scavenging enzymes catalase and ascorbate peroxidase, (ii) a high affinity SA-binding protein (SABP2), (iii) a SA-inducible protein kinase (SIPK), (iv) NPR1, an ankyrin repeat-containing protein that exhibits limited homology to IkappaBalpha and is required for SA signaling, and (v) members of the TGA/OBF family of bZIP transcription factors. These bZIP factors physically interact with NPR1 and bind the SA-responsive element in promoters of several defense genes, such as the pathogenesis-related 1 gene (PR-1). Recent studies have demonstrated that nitric oxide (NO) is another signal that activates defense responses after pathogen attack. NO has been shown to play a critical role in the activation of innate immune and **inflammatory** responses in animals. Increases in NO synthase (NOS)-like activity occurred in resistant but not susceptible tobacco after infection with tobacco mosaic virus. Here we demonstrate that this increase in activity participates in PR-1 gene induction. Two signaling molecules, cGMP and cyclic ADP ribose (**cADPR**), which function downstream of NO in animals, also appear to mediate plant defense gene activation (e.g., PR-1). Additionally, NO may activate PR-1 expression via an NO-dependent, **cADPR**-independent pathway. Several targets of NO in animals, including guanylate cyclase, aconitase, and mitogen-activated protein kinases (e.g., SIPK), are also modulated by NO in plants. Thus, at least portions of NO signaling pathways appear to be shared between plants and animals.

L2 ANSWER 20 OF 22 MEDLINE on STN
ACCESSION NUMBER: 1999156161 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10048416
TITLE: Retinoid-mediated signaling pathways in CD38 antigen expression in myeloid leukemia cells.
AUTHOR: Mehta K; Cheema S
CORPORATE SOURCE: Department of Bioimmunotherapy, The University of Texas M.D. Anderson Cancer Center, Houston 77030, USA.. kmehta@mdacc.tmc.edu
CONTRACT NUMBER: FDR-000923 (FDA)
SOURCE: Leukemia & lymphoma, (1999 Feb) Vol. 32, No. 5-6, pp. 441-9. Ref: 65
Journal code: 9007422. ISSN: 1042-8194.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 4 May 1999
Last Updated on STN: 18 Dec 2002
Entered Medline: 20 Apr 1999

AB The lymphocyte cell surface antigen CD38, which was originally described as a differentiation marker, has emerged as an important multifunctional protein. Its most intriguing and well characterized function is its ability to catalyze the synthesis of cyclic ADP-ribose (**cADPR**) from NAD. **cADPR** serves as an important second messenger in controlling the release of intracellular calcium from ryanodine-sensitive intracellular pools. By virtue of its ability to synthesize **cADPR** as well as to act as an adhesion and signal transduction molecule, CD38 may play a role in such diverse physiological processes as cell growth, apoptosis, differentiation, and **inflammation**. Equally interesting is the pattern of CD38 expression in hematopoietic cells. In the bone marrow, early precursor cells predominantly express CD38 antigen, whereas mature circulating blood cells lack or express very low levels. The expression is also high on malignant hematopoietic cells and thus may be of prognostic relevance in certain leukemias. Presently, there is little information available on the factors that regulate the expression of CD38 antigen in hematopoietic cells. In this review, we summarize recent findings on the regulation of CD38 antigen by retinoids (vitamin A and related compounds). At least in the myeloid cell lineage, retinoids

appear to be exquisitely potent and specific inducers of CD38 antigen expression, and retinoid-induced expression of CD38 is mediated via activation of the retinoic acid-alpha (RAR alpha) nuclear receptor.

L2 ANSWER 21 OF 22 MEDLINE on STN
ACCESSION NUMBER: 97332695 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9188506
TITLE: Role of cyclic ADP-ribose in ATP-activated potassium currents in alveolar macrophages.
AUTHOR: Ebihara S; Sasaki T; Hida W; Kikuchi Y; Oshiro T; Shimura S; Takasawa S; Okamoto H; Nishiyama A; Akaike N; Shirato K
CORPORATE SOURCE: First Department of Internal Medicine, Tohoku University School of Medicine, Sendai 980-77, Japan.
SOURCE: The Journal of biological chemistry, (1997 Jun 20) Vol. 272, No. 25, pp. 16023-9.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199707
ENTRY DATE: Entered STN: 5 Aug 1997
Last Updated on STN: 10 Dec 2002
Entered Medline: 21 Jul 1997

AB There is growing evidence that extracellular ATP causes a dramatic change in the membrane conductance of a variety of **inflammatory** cells. In the present study, using the nystatin perforated patch recording configuration, we found that ATP (0.3-30 microM) induced a transient outward current in a concentration-dependent manner and that the reversal potential of the ATP-induced outward current was close to the K+ equilibrium potential, indicating that the membrane behaves like a K+ electrode in the presence of ATP. The first application of ATP to alveolar macrophages perfused with Ca2+-free external solution could induce the outward current, but the response to ATP was diminished with successive applications. Intracellular perfusion with a Ca2+ chelator, 1,2-bis(2-aminophenoxy)ethane-N,N,N', N'-tetraacetic acid, also diminished the response. When cyclic ADP-ribose (**cADPR**) was applied to the macrophage cytoplasm, a transient outward current was elicited. Thereafter, the successive outward current was inhibited, suggesting the involvement of **cADPR** in the response. Intracellular perfusion with inositol 1,4, 5-trisphosphate also induced a transient outward current, but the successive current was not inhibited. The ATP-induced outward current was abolished when 8-amino-**cADPR** (as a blocker of **cADPR**, 10(-6)-10(-5) M) was introduced into the cytoplasm. Homogenates of alveolar macrophages showed both ADP-ribosyl cyclase and **cADPR** hydrolase activities, and CD38 (ADP-ribosyl cyclase/ **cADPR** hydrolase) expression was confirmed by reverse transcriptase-polymerase chain reaction and Western blot analyses. These results indicate that ATP activates K+ currents by releasing Ca2+ from **cADPR**-sensitive internal Ca2+ stores.

L2 ANSWER 22 OF 22 MEDLINE on STN
ACCESSION NUMBER: 96106570 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8529265
TITLE: The whoosh and trickle of calcium signalling.
AUTHOR: Murphy C T; Poll C T; Westwick J
CORPORATE SOURCE: Department of Pharmacology, School of Pharmacy and Pharmacology, University of Bath, Avon, UK.
SOURCE: Cell calcium, (1995 Sep) Vol. 18, No. 3, pp. 245-51.
Journal code: 8006226. ISSN: 0143-4160.
PUB. COUNTRY: SCOTLAND: United Kingdom
DOCUMENT TYPE: Conference; Conference Article; (CONGRESSES)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 199601
ENTRY DATE: Entered STN: 20 Feb 1996
Last Updated on STN: 29 Jan 1999
Entered Medline: 29 Jan 1996

AB The importance of phospholipase C catalysed hydrolysis of phosphatidylinositol-(4,5)bisphosphate (PtdIns(4,5)P2) to inositol-(1,4,5)trisphosphate (Ins(1,4,5)P3) and sn-1,2-diacylglycerol in the signal transduction pathways of eukaryote cells, in response to extracellular stimuli, is now widely recognised. Although nearly 60 naturally occurring inositol phosphates have been identified in mammalian cells, mobilisation of Ca2+ from the intracellular stores has been most commonly attributed to the generation of Ins(1,4,5)P3 [1]. However, there is increasing evidence for the presence of ryanodine receptors (RyR) in non-excitable cells and for cADP-ribose (**cADPr**) as the signalling molecule responsible for Ca2+ release via the RyR. But what is the purpose for the co-existence of these two intracellular Ca2+ channels in non-excitable cells and why are they so heterogeneous in their distribution? These questions were explored at the recent International Symposium Calcium Signalling in **Inflammatory** Cells. Depletion of the intracellular Ca2+ pools is followed by entry of Ca2+ into the cell across the plasma membrane, but the mechanism(s) underlying this 'capacitative Ca2+ entry' is not well understood. Many potential signalling pathways which may account for capacitative Ca2+ entry have been proposed although none have been unanimously accepted. New developments in the elucidation of the mechanism responsible for capacitative Ca2+ entry and how Ca2+ entry is regulated, together with progress in the characterisation of plasma membrane Ca2+ entry channels were also discussed at this symposium.

L2 ANSWER 8 OF 22 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:946087 CAPLUS
DOCUMENT NUMBER: 138:11408
TITLE: ADP ribosyl cyclase inhibitors for treating autoimmune and inflammatory disorders
INVENTOR(S): Potter, Barry V. L.; Guse, Andreas H.; Mayr, Georg W.; Schweitzer, Katrin
PATENT ASSIGNEE(S): University of Bath, UK
SOURCE: PCT Int. Appl., 64 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002098397	A2	20021212	WO 2002-GB2695	20020606
WO 2002098397	A3	20030313		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
GB 2392095	A1	20040225	GB 2003-28165	20020606
EP 1395267	A2	20040310	EP 2002-735614	20020606
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2004214789	A1	20041028	US 2003-730589	20031208
PRIORITY APPLN. INFO.:			GB 2001-13923 A	20010607
			WO 2002-GB2695 W	20020606

OTHER SOURCE(S): MARPAT 138:11408

AB The use of a compound of formula A-L-B wherein A and B are independently selected from a cyclic ring, wherein each of which cyclic rings A and B may be optionally substituted at at least one ring position; and L is a suitable linker; or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in inhibiting ADP-ribosyl cyclase.

L2 ANSWER 1 OF 22 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1061061 CAPLUS
DOCUMENT NUMBER: 143:419493
TITLE: Non-specific effects of 4-chloro-m-cresol may cause calcium flux and respiratory burst in human neutrophils
AUTHOR(S): Hauser, Carl J.; Kannan, Kolenkode B.; Deitch, Edwin A.; Itagaki, Kiyoshi
CORPORATE SOURCE: Department of Surgery, Division of Trauma, UMDNJ-New Jersey Medical School, Newark, NJ, 07103, USA
SOURCE: Biochemical and Biophysical Research Communications (2005), 336(4), 1087-1095
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We examined the effects of 4-chloro-m-cresol (4-CmC, a potent and specific activator of ryanodine receptors) on Ca2+-release/influx and respiratory burst in freshly isolated human PMN as well as HL60 cells. 4-CmC induces Ca2+ store-depletion in a dose-dependent manner at concns. between 400 μM and 3 mM, however no dose-dependent effect on Ca2+-influx was found. 4-CmC depleted Ca2+ stores that were shared with the GPC agonists such as fMLP and PAF, and therefore 4-CmC presumably depletes Ca2+ from ER. Since the authentic ligand for RyR is cyclic ADP-ribose (**cADPR**), we assessed the functional relevance of RyR in PMN by studying the presence and function of membrane-bound ADP-ribosyl cyclase (CD38) in PMN. First, expression of CD38 was confirmed by RT-PCR using cDNA from HL60 cells. Second, PMN from trauma patients showed significantly enhanced CD38 expression than those from healthy volunteers. In addition, although no chemotaxis effect was detected by 4-CmC, it stimulated respiratory burst in PMN in a dose-dependent manner. Our findings suggest that RyRs exist in human PMN and that RyR pathway may play an active role in **inflammatory** PMN calcium signaling. 8-Br-**cADPR** and cyclic 3-deaza-ADP did not have inhibitory effects either on 4-CmC-induced Ca2+ store-depletion or on respiratory burst, on the other hand, PLC inhibitor, U73122, completely attenuated both 4-CmC-induced Ca2+ store-depletion and respiratory burst. Although it has been used as a specific activator of RyR, 4-CmC has non-specific effects which cause Ca2+ store-depletion and respiratory burst at least in human PMN.
REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 2 OF 22 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:259650 CAPLUS
DOCUMENT NUMBER: 142:291376
TITLE: Extracellular NAD+ and cyclic adenosine diphosphate ribose (cADPR) as potent antiinflammatory agents
INVENTOR(S): Fink, Mitchell P.; Delude, Russell L.; Han, Xianonan
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 18 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005065109	A1	20050324	US 2003-659063	20030910
PRIORITY APPLN. INFO.:			US 2003-659063	20030910

AB A method of prophylaxis or treatment of **inflammatory** conditions, including, but not limited to, intestinal epithelial **inflammation** due to intestine-specific conditions (e.g., Crohn's disease or ulcerative

colitis) or systemic causes of **inflammation** (e.g., endotoxemia, sepsis, hemorrhagic shock/resuscitation or pancreatitis) is disclosed. In the method, an affected patient is administered a therapeutically effective amount of a composition including an NAD-related compound, in a form that is accessible to a receptor mol., conveyed in a pharmaceutically acceptable carrier vehicle. NAD-related compds. include NAD (NAD+), cyclic ADP ribose (**cADPR**), or functionally equivalent analogs, derivs., metabolites or agonists thereof, or prodrugs therefor. Also disclosed are ex vivo and in vivo assay methods to test candidate compds. for activity, kits for carrying out the therapeutic methods or the assay methods of the invention and articles of manufacture that include compns. for use in the methods of the invention and instructions for the use thereof.

L2 ANSWER 3 OF 22 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:608702 CAPLUS
DOCUMENT NUMBER: 141:205426
TITLE: Tumor necrosis factor-α differentially regulates the expression of proinflammatory genes in human airway smooth muscle cells by activation of interferon-β-dependent CD38 pathway
AUTHOR(S): Tliba, Omar; Panettieri, Reynold A., Jr.; Tliba, Samira; Walseth, Timothy F.; Amrani, Yassine
CORPORATE SOURCE: Pulmonary, Allergy, and Critical Care Division, Department of Medicine, University of Pennsylvania Medical Center, Philadelphia, PA, USA
SOURCE: Molecular Pharmacology (2004), 66(2), 322-329
CODEN: MOPMA3; ISSN: 0026-895X
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Recent evidence suggests that CD38, an ectoenzyme that converts NAD+ to cyclic ADP-ribose (**cADPr**), may play a role in cytokine-induced airway smooth muscle (ASM) cell hyper-responsiveness, a key feature associated with chronic asthma. In the present study, the authors investigated the major signaling pathways by which tumor necrosis factor-α (TNFα) induces CD38 expression and its role in regulating gene expression in human ASM cells. Using flow cytometry analyses, TNFα enhanced CD38 expression in a manner that was time- (0-24 h), concentration- (0.1-40 ng/mL), and protein synthesis- (cycloheximide blockade) dependent. A selective agonistic antibody against tumor necrosis factor receptor (TNFR) 1 also augmented CD38 expression, whereas anti-TNFR2 antagonistic antibody did not prevent the TNFα response. Inhibition of the Janus activated kinase/signal transducer and activator of transcription pathways using the soluble inhibitor 2-(1,1-dimethylethyl)-9-fluoro-3,6-dihydro-7H-benz-[h]imidaz[4,5-f]isoquinolin-7-one (DBI) or with neutralizing antibody against interferon β (IFNβ) completely abrogated TNFα-induced CD38 expression at both protein and mRNA levels. Combining TNFα (0.1 and 1 ng/mL) and IFNβ (100 IU/mL) at concns. alone that had little effect on CD38 expression induced a robust synergistic induction of CD38 mRNA and protein levels. 8-Bromo-**cADPr**, a **cADPr** antagonist, significantly augmented TNFα-induced interleukin-6 secretion, whereas regulated on activation normal T cell expressed and secreted secretion was suppressed. 8-Bromo-**cADPr**, however, did not affect TNFα-induced cell surface expression of intercellular adhesion mol.-1. The authors' study is the first to demonstrate that IFNβ-dependent activation of CD38 pathway is a novel component by which TNFα differentially regulates the expression of **inflammatory** genes in ASM cells.

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 4 OF 22 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:266248 CAPLUS
DOCUMENT NUMBER: 140:286134
TITLE: Regulation of dendritic cell trafficking by the ADP-ribosyl cyclase CD38: impact on the development of humoral immunity
AUTHOR(S): Partida-Sanchez, Santiago; Goodrich, Stephen; Kusser, Kim; Oppenheimer, Norman; Randall, Troy D.; Lund, Frances E.
CORPORATE SOURCE: Trudeau Institute, Saranac Lake, NY, 12983, USA
SOURCE: Immunity (2004), 20(3), 279-291
CODEN: IUNIEH; ISSN: 1074-7613
PUBLISHER: Cell Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Mice lacking CD38, an ectoenzyme that generates the calcium-mobilizing metabolite **cADPR**, make reduced T cell-dependent antibody responses. Despite the predicted role for CD38 in B cell activation, we find that CD38 regulates the migration of dendritic cell (DC) precursors from the blood to peripheral sites and controls the migration of mature DCs from sites of **inflammation** to lymph nodes. Thus, T cells are inefficiently primed in Cd38-/- mice, leading to poor humoral immune responses. We also show that CD38 and **cADPR** modulate calcium mobilization in chemokine-stimulated DCs and are required for the chemotaxis of immature and mature DCs to CCL2, CCL19, CCL21, and CXCL12. Therefore, CD38 regulates adaptive immunity by controlling chemokine receptor signaling in DCs.
REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 5 OF 22 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:93934 CAPLUS
DOCUMENT NUMBER: 140:162333
TITLE: Chemotaxis and calcium responses of phagocytes to formyl peptide receptor ligands is differentially regulated by cyclic ADP ribose
AUTHOR(S): Partida-Sanchez, Santiago; Iribarren, Pablo; Moreno-Garcia, Miguel E.; Gao, Ji-Liang; Murphy, Philip M.; Oppenheimer, Norman; Wang, Ji Ming; Lund, Frances E.
CORPORATE SOURCE: Trudeau Institute, Saranac Lake, NY, 12983, USA
SOURCE: Journal of Immunology (2004), 172(3), 1896-1906
CODEN: JOIMA3; ISSN: 0022-1767
PUBLISHER: American Association of Immunologists
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Cyclic ADP ribose (**cADPR**) is a calcium-mobilizing metabolite that regulates intracellular calcium release and extracellular calcium influx. Although the role of **cADPR** in modulating calcium mobilization has been extensively examined, its potential role in regulating immunol. responses is less well understood. The authors previously reported that **cADPR**, produced by the ADP-ribosyl cyclase, CD38, controls calcium influx and chemotaxis of murine neutrophils responding to fMLF, a peptide agonist for two chemoattractant receptor subtypes, formyl peptide receptor and formyl peptide receptor-like 1. Here, they examine whether **cADPR** is required for chemotaxis of human monocytes and neutrophils to a diverse array of chemoattractants. They found that a **cADPR** antagonist and a CD38 substrate analog inhibited the chemotaxis of human phagocytic cells to a number of formyl peptide receptor-like 1-specific ligands but had no effect on the chemotactic response of these cells to ligands selective for formyl peptide receptor. In addition, the authors show that the **cADPR** antagonist blocks the chemotaxis of human monocytes to CXCR4, CCR1, and CCR5 ligands. In all cases, the authors found that **cADPR** modulates intracellular free calcium levels in cells activated by chemokines that induce extracellular

calcium influx in the apparent absence of intracellular calcium release. Thus, **cADPR** regulates calcium signaling of a discrete subset of chemoattractant receptors expressed by human leukocytes. Since many of the chemoattractant receptors regulated by **cADPR** bind to ligands that are associated with clin. pathol., **cADPR** and CD38 represent novel drug targets with potential application in chronic **inflammatory** and neurodegenerative disease.

REFERENCE COUNT: 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 6 OF 22 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:744512 CAPLUS
DOCUMENT NUMBER: 140:403778
TITLE: Calcium regulation in smooth muscle through the CD38/cyclic ADP-ribose pathway
AUTHOR(S): White, Thomas A.; Deshpande, Deepak A.; Dogan, Soner; Panettieri, Reynold A.; Walseth, Timothy F.; Kannan, Mathur S.
CORPORATE SOURCE: Department of Veterinary PathoBiology, College of Veterinary Medicine, University of Minnesota, St. Paul, MN, USA
SOURCE: Cyclic ADP-Ribose and NAADP (2002), 427-449. Editor(s): Lee, Hon Cheung. Kluwer Academic Publishers: Norwell, Mass. CODEN: 69ENI2; ISBN: 1-4020-7281-3
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A review on the role of the CD38/cyclic ADP-ribose (**cADPR**) pathway of Ca2+ regulation in airway, vascular, uterine, and intestinal smooth muscles. Evidence for regulation of CD38 expression in smooth muscles by hormones and **inflammatory** mediators is provided. The mechanisms by which **cADPR** causes Ca2+ release from the sarcoplasmic reticulum in different smooth muscles are also discussed.
REFERENCE COUNT: 100 THERE ARE 100 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 7 OF 22 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:212944 CAPLUS
DOCUMENT NUMBER: 138:367397
TITLE: CD38-cyclic ADP-ribose-mediated Ca2+ signaling contributes to airway smooth muscle hyperresponsiveness
AUTHOR(S): Deshpande, Deepak A.; Walseth, Timothy F.; Panettieri, Reynold A.; Kannan, Mathur S.
CORPORATE SOURCE: Departments of Veterinary PathoBiology and Pharmacology, University of Minnesota, St. Paul, MN, 55108, USA
SOURCE: FASEB Journal (2003), 17(3), 452-454, 10.1096/fj.02-0450fje CODEN: FAJOEC; ISSN: 0892-6638
PUBLISHER: Federation of American Societies for Experimental Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We previously demonstrated that cyclic ADP-ribose (**cADPR**) elicits Ca2+ release in airway smooth muscle (ASM) cells through ryanodine receptor channels. CD38 is a cell surface protein that catalyzes the synthesis and degradation of **cADPR**. In **inflammatory** diseases such as asthma, augmented Ca2+ responses and Ca2+ sensitivity contribute to increased ASM contractility in response to agonists. In this study, we investigated the regulation of CD38 expression and the role of **cADPR**-mediated Ca2+ release in airway **inflammation**. Human ASM cells in culture between the second and fifth passages were

exposed to tumor necrosis factor α (TNF-α), interleukin 1β, or interferon γ, or bovine serum albumin (controls). CD38 expression was measured by reverse transcriptase-polymerase chain reaction (RT-PCR), real-time PCR, and Western blot anal., and ADP-ribosyl cyclase activity was assayed with nicotinamide guanine dinucleotide as the substrate. Ca2+ responses to acetylcholine, bradykinin, and thrombin were measured in fura-2AM-loaded cells by fluorescence microscopy. Cytokines caused significant augmentation of CD38 expression, ADP-ribosyl cyclase activity, and Ca2+ responses to the agonists, compared with the control. TNF-α effects were greater than those of the other two cytokines. The **cADPR** antagonist 8-bromo-**cADPR** attenuated the Ca2+ responses to the agonists in control and cytokine-treated cells, with the magnitude of inhibition correlating with the level of CD38. This study provides the first demonstration of a role for CD38-**cADPR** signaling in a model of **inflammatory** airway disease.

REFERENCE COUNT: 65 THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 8 OF 22 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:946087 CAPLUS
DOCUMENT NUMBER: 138:11408
TITLE: ADP ribosyl cyclase inhibitors for treating autoimmune and inflammatory disorders
INVENTOR(S): Potter, Barry V. L.; Guse, Andreas H.; Mayr, Georg W.; Schweitzer, Katrin
PATENT ASSIGNEE(S): University of Bath, UK
SOURCE: PCT Int. Appl., 64 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002098397	A2	20021212	WO 2002-GB2695	20020606
WO 2002098397	A3	20030313		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
GB 2392095	A1	20040225	GB 2003-28165	20020606
EP 1395267	A2	20040310	EP 2002-735614	20020606
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2004214789	A1	20041028	US 2003-730589	20031208

PRIORITY APPLN. INFO.: GB 2001-13923 A 20010607
WO 2002-GB2695 W 20020606

OTHER SOURCE(S): MARPAT 138:11408

AB The use of a compound of formula A-L-B wherein A and B are independently selected from a cyclic ring, wherein each of which cyclic rings A and B may be optionally substituted at at least one ring position; and L is a suitable linker; or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in inhibiting ADP-ribosyl cyclase.

L2 ANSWER 9 OF 22 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:569665 CAPLUS
DOCUMENT NUMBER: 133:249795

TITLE: Nitric oxide and salicylic acid signaling in plant defense
AUTHOR(S): Klessig, Daniel F.; Durner, Jorg; Noad, Robert; Navarre, Duroy A.; Wendehenne, David; Kumar, Dhirendra; Zhou, Jun Ma; Shah, Jyoti; Zhang, Shuqun; Kachroo, Pradeep; Trifa, Youssef; Pontier, Dominique; Lam, Eric; Silva, Herman
CORPORATE SOURCE: Waksman Institute and Department of Molecular Biology and Biochemistry, Rutgers, The State University of New Jersey, Piscataway, NJ, 08854-8020, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2000), 97(16), 8849-8855
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Salicylic acid (SA) plays a critical signaling role in the activation of plant defense responses after pathogen attack. Several potential components of the SA signaling pathway were identified, including (i) the H2O2-scavenging enzymes catalase and ascorbate peroxidase, (ii) a high affinity SA-binding protein (SABP2), (iii) a SA-inducible protein kinase (SIPK), (iv) NPR1, an ankyrin repeat-containing protein that exhibits limited homol. to IκBα and is required for SA signaling, and (v) members of the TGA/OBF family of bZIP transcription factors. These bZIP factors phys. interact with NPR1 and bind the SA-responsive element in promoters of several defense genes, such as the pathogenesis-related 1 gene (PR-1). Nitric oxide (NO) is another signal that activates defense responses after pathogen attack. NO plays a critical role in the activation of innate immune and **inflammatory** responses in animals. Increases in NO synthase (NOS)-like activity occurred in resistant but not susceptible tobacco after infection with tobacco mosaic virus. Here we demonstrate that this increase in activity participates in PR-1 gene induction. Two signaling mols., cGMP and cyclic ADP ribose (**cADPR**), which function downstream of NO in animals, also appear to mediate plant defense gene activation (e.g., PR-1). Addnl., NO may activate PR-1 expression via an NO-dependent, **cADPR**-independent pathway. Several targets of NO in animals, including guanylate cyclase, aconitase, and mitogen-activated protein kinases (e.g., SIPK), are also modulated by NO in plants. Thus, at least portions of NO signaling pathways appear to be shared between plants and animals.
REFERENCE COUNT: 75 THERE ARE 75 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 10 OF 22 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:550743 CAPLUS
DOCUMENT NUMBER: 134:114370
TITLE: Retinoid-mediated signaling pathways in CD38 antigen expression in myeloid leukemia cells
AUTHOR(S): Mehta, Kapil; Cheema, Sangeeta
CORPORATE SOURCE: Department of Bioimmunotherapy, The University of Texas M.D. Anderson Cancer Center, Houston, TX, 77030, USA
SOURCE: Leukemia & Lymphoma (1999), 32(5/6), 441-449
CODEN: LELYEA; ISSN: 1042-8194
PUBLISHER: Harwood Academic Publishers
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 65 refs. The lymphocyte cell surface antigen CD38, which was originally described as a differentiation marker, has emerged as an important multifunctional protein. Its most intriguing and well characterized function is its ability to catalyze the synthesis of cyclic ADP-ribose (**cADPR**) from NAD. **CADPR** serves as an important second messenger in controlling the release of intracellular calcium from ryanodine-sensitive intracellular pools. By virtue of its

ability to synthesize **cADPR** as well as to act as an adhesion and signal transduction mol., CD38 may play a role in such diverse physiol. processes as cell growth, apoptosis, differentiation, and **inflammation**. Equally interesting is the pattern of CD38 expression in hematopoietic cells. In the bone marrow, early precursor cells predominantly express CD38 antigen, whereas mature circulating blood cells lack or express very low levels. The expression is also high on malignant hematopoietic cells and thus may be of prognostic relevance in certain leukemias. Presently, there is little information available on the factors that regulate the expression of CD38 antigen in hematopoietic cells. In this review, we summarize recent findings on the regulation of CD38 antigen by retinoids (vitamin A and related compds.). At least in the myeloid cell lineage, retinoids appear to be exquisitely potent and specific inducers of CD38 antigen expression, and retinoid-induced expression of CD38 is mediated via activation of the retinoic acid-alpha (RARα) nuclear receptor.

REFERENCE COUNT: 65 THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:259650 CAPLUS
DOCUMENT NUMBER: 142:291376
TITLE: Extracellular NAD+ and cyclic adenosine diphosphate ribose (cADPR) as potent antiinflammatory agents
INVENTOR(S): Fink, Mitchell P.; Delude, Russell L.; Han, Xianonan
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 18 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005065109	A1	20050324	US 2003-659063	20030910
PRIORITY APPLN. INFO.:			US 2003-659063	20030910

AB A method of prophylaxis or treatment of inflammatory conditions, including, but not limited to, intestinal epithelial inflammation due to intestine-specific conditions (e.g., Crohn's disease or ulcerative colitis) or systemic causes of inflammation (e.g., **endotoxemia**, sepsis, hemorrhagic shock/resuscitation or pancreatitis) is disclosed. In the method, an affected patient is administered a therapeutically effective amount of a composition including an NAD-related compound, in a form that is accessible to a receptor mol., conveyed in a pharmaceutically acceptable carrier vehicle. NAD-related compds. include NAD (NAD+), cyclic ADP ribose (**cADPR**), or functionally equivalent analogs, derivs., metabolites or agonists thereof, or prodrugs therefor. Also disclosed are ex vivo and in vivo assay methods to test candidate compds. for activity, kits for carrying out the therapeutic methods or the assay methods of the invention and articles of manufacture that include compns. for use in the methods of the invention and instructions for the use thereof.

L4 ANSWER 1 OF 12 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:33420 CAPLUS
DOCUMENT NUMBER: 144:106359
TITLE: IL-4 inhibits calcium transients in bovine trachealis cells by a ryanodine receptor dependent mechanism
AUTHOR(S): Ethier, Michael F.; Madison, J. Mark
CORPORATE SOURCE: Department of Medicine, University of Massachusetts Medical School, Worcester, MA, 01605, USA
SOURCE: FASEB Journal (2006), 20(1), 154-156, 10.1096/fj.05-4031fje
CODEN: FAJOEC; ISSN: 0892-6638
PUBLISHER: Federation of American Societies for Experimental Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB IL-4 and IL-13 have important roles in the pathogenesis of **asthma**. A novel finding was that brief exposure of airway smooth muscle cells to IL-4 inhibited carbachol-stimulated calcium transients. The authors hypothesized that IL-4 inhibits transients by decreasing calcium store content and tested this by measuring the effects of IL-4 on transients induced by a nonspecific ionophore. Bovine trachealis cells were loaded with fura 2-AM, and cytosolic calcium concns. ([Ca2+]i) were measured in single cells by digital microscopy. Stimulation (SI) with carbachol (10 μM) caused rapid, transient increases in [Ca2+]i to 1299 355 nM. After recovery of calcium stores, stimulation (S2) of the same cells with ionomycin (10 μM), in the absence of extracellular calcium, also increased [Ca2+]i to give S2/S1 ratio of 1.03. However, after 20 min of IL-4 (50 ng/mL), but not IL-13, ionomycin transients were decreased to 0.50 (S2/S1). IL-4 did not inhibit transients with ryanodine receptor calcium release channels (RyR) blocked by ryanodine (200 μM) (S2/S1=1.01) but still did in the presence of 8-bromo cyclic ADP-ribose, an antagonist of cyclic ADP-ribose (**cADPR**) signaling at RyR (S2/S1=0.48). Together, findings suggest that IL-4 decreases intracellular calcium stores by mechanisms dependent on RyR, but not on **cADPR** signaling.
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 12 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:430445 CAPLUS
DOCUMENT NUMBER: 142:444868
TITLE: CD38/cyclic ADP-ribose signaling: Role in the regulation of calcium homeostasis in airway smooth muscle
AUTHOR(S): Deshpande, Deepak A.; White, Thomas A.; Dogan, Soner; Walseth, Timothy F.; Panettieri, Reynold A.; Kannan, Mathur S.
CORPORATE SOURCE: Departments of Veterinary and Biomedical Sciences, University of Minnesota, Saint Paul, MN, USA
SOURCE: American Journal of Physiology (2005), 288(5, Pt. 1), L773-L788
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. The contractility of airway smooth muscle cells is dependent on dynamic changes in the concentration of intracellular calcium. Signaling mols. such as inositol 1,4,5-trisphosphate and cyclic ADP-ribose play pivotal roles in the control of intracellular calcium concentration Alterations in the processes involved in the regulation of intracellular calcium concentration contribute to the pathogenesis of airway diseases such as **asthma**. Recent studies have identified cyclic ADP-ribose as a calcium-mobilizing second messenger in airway smooth muscle cells, and

modulation of the pathway involved in its metabolism results in altered calcium homeostasis and may contribute to airway hyperresponsiveness. In this review, we describe the basic mechanisms underlying the dynamics of calcium regulation and the role of CD38/**cADPR**, a novel pathway, in the context of airway smooth muscle function and its contribution to airway diseases such as **asthma**.

REFERENCE COUNT: 178 THERE ARE 178 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 12 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:608702 CAPLUS

DOCUMENT NUMBER: 141:205426

TITLE: Tumor necrosis factor-α differentially regulates the expression of proinflammatory genes in human airway smooth muscle cells by activation of interferon-β-dependent CD38 pathway

AUTHOR(S): Tliba, Omar; Panettieri, Reynold A., Jr.; Tliba, Samira; Walseth, Timothy F.; Amrani, Yassine

CORPORATE SOURCE: Pulmonary, Allergy, and Critical Care Division, Department of Medicine, University of Pennsylvania Medical Center, Philadelphia, PA, USA

SOURCE: Molecular Pharmacology (2004), 66(2), 322-329
CODEN: MOPMA3; ISSN: 0026-895X

PUBLISHER: American Society for Pharmacology and Experimental Therapeutics

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Recent evidence suggests that CD38, an ectoenzyme that converts NAD+ to cyclic ADP-ribose (**cADPr**), may play a role in cytokine-induced airway smooth muscle (ASM) cell hyper-responsiveness, a key feature associated with chronic **asthma**. In the present study, the authors investigated the major signaling pathways by which tumor necrosis factor-α (TNFα) induces CD38 expression and its role in regulating gene expression in human ASM cells. Using flow cytometry analyses, TNFα enhanced CD38 expression in a manner that was time- (0-24 h), concentration- (0.1-40 ng/mL), and protein synthesis- (cycloheximide blockade) dependent. A selective agonistic antibody against tumor necrosis factor receptor (TNFR) 1 also augmented CD38 expression, whereas anti-TNFR2 antagonistic antibody did not prevent the TNFα response. Inhibition of the Janus activated kinase/signal transducer and activator of transcription pathways using the soluble inhibitor 2-(1,1-dimethylethyl)-9-fluoro-3,6-dihydro-7H-benz-[h]imidaz[4,5-f]isoquinolin-7-one (DBI) or with neutralizing antibody against interferon β (IFNβ) completely abrogated TNFα-induced CD38 expression at both protein and mRNA levels. Combining TNFα (0.1 and 1 ng/mL) and IFNβ (100 IU/mL) at concns. alone that had little effect on CD38 expression induced a robust synergistic induction of CD38 mRNA and protein levels. 8-Bromo-**cADPr**, a **cADPr** antagonist, significantly augmented TNFα-induced interleukin-6 secretion, whereas regulated on activation normal T cell expressed and secreted secretion was suppressed. 8-Bromo-**cADPr**, however, did not affect TNFα-induced cell surface expression of intercellular adhesion mol.-1. The authors' study is the first to demonstrate that IFNβ-dependent activation of CD38 pathway is a novel component by which TNFα differentially regulates the expression of inflammatory genes in ASM cells.

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 12 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:556028 CAPLUS

DOCUMENT NUMBER: 141:241927

TITLE: Modulation of calcium signaling by interleukin-13 in human airway smooth muscle: Role of CD38/cyclic

adenosine diphosphate ribose pathway
AUTHOR(S): Deshpande, Deepak A.; Dogan, Soner; Walseth, Timothy F.; Miller, Steven M.; Amrani, Yassine; Panettieri, Reynold A.; Kannan, Mathur S.
CORPORATE SOURCE: Departments of Veterinary PathoBiology and Pharmacology, University of Minnesota, St. Paul, MN, USA
SOURCE: American Journal of Respiratory Cell and Molecular Biology (2004), 31(1), 36-42
CODEN: AJRBEL; ISSN: 1044-1549
PUBLISHER: American Thoracic Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB CD38/cyclic ADP ribose (**cADPR**) signaling plays an important role in the regulation of intracellular calcium responses to agonists in a variety of cells, including airway smooth muscle (ASM) cells. The present study was aimed at determining the effect of interleukin (IL)-13, a cytokine implicated in the pathogenesis of **asthma**, on CD38/**cADPR** signaling and to ascertain the contribution of CD38/**cADPR** signaling to IL-13-induced airway hyperresponsiveness. Human ASM cells maintained in culture were exposed to 50 ng/mL IL-13 for 22 h and levels of CD38 expression and intracellular calcium responses to agonists were measured. Treatment of human ASM cells with IL-13 resulted in increased CD38 expression as determined by real-time polymerase chain reaction, Western blot anal., and indirect immunofluorescence. Increased CD38 expression was reflected as increased ADP-ribosyl cyclase activity in the ASM cell membranes. The net intracellular calcium responses to bradykinin, thrombin, and histamine were significantly higher in cells treated with IL-13 compared with controls. Furthermore, 8-bromo-**cADPR**, a **cADPR** antagonist, attenuated IL-13-induced augmented intracellular calcium responses to agonists in human ASM cells. These findings indicate that the CD38/**cADPR**-dependent pathway has a major role in IL-13-induced modulation of calcium signaling in human ASM.
REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 12 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:406899 CAPLUS
DOCUMENT NUMBER: 141:69063
TITLE: Bronchial hyperresponsiveness: insights into new signaling molecules
AUTHOR(S): Amrani, Yassine; Tliba, Omar; Deshpande, Deepak A.; Walseth, Timothy F.; Kannan, Mathur S.; Panettieri, Reynold A.
CORPORATE SOURCE: Department of Medicine, Allergy and Critical Care Division, Pulmonary, University of Pennsylvania Medical Center, Philadelphia, PA, 19104, USA
SOURCE: Current Opinion in Pharmacology (2004), 4(3), 230-234
CODEN: COPUBK; ISSN: 1471-4892
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Signaling mols. play a critical role in the pathophysiol. of airway diseases. Recent evidence shows that cyclic ADP-ribose (**cADPr**), an endogenous activator of the ryanodine receptor channel in mammalian cells, modulates agonist-induced calcium responses in airway smooth muscle (ASM) cells. In addition, **cADPr**-mediated calcium release appears to play an important role in the non-specific' increased ASM responsiveness to contractile agonists in cytokine-treated cells, a characteristic finding of **asthma**. Furthermore, other signaling mols. such as Rho/Rho kinase and phosphodiesterase also contribute to bronchial hyperresponsiveness. Thus, a better understanding of these signaling mols. that alter calcium signaling and contractility of ASM might provide new insight into novel therapeutic targets for the control

of bronchial hyperresponsiveness.
REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 12 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:212944 CAPLUS
DOCUMENT NUMBER: 138:367397
TITLE: CD38-cyclic ADP-ribose-mediated Ca2+ signaling contributes to airway smooth muscle hyperresponsiveness
AUTHOR(S): Deshpande, Deepak A.; Walseth, Timothy F.; Panettieri, Reynold A.; Kannan, Mathur S.
CORPORATE SOURCE: Departments of Veterinary PathoBiology and Pharmacology, University of Minnesota, St. Paul, MN, 55108, USA
SOURCE: FASEB Journal (2003), 17(3), 452-454, 10.1096/fj.02-0450fje
CODEN: FAJOEC; ISSN: 0892-6638
PUBLISHER: Federation of American Societies for Experimental Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We previously demonstrated that cyclic ADP-ribose (**cADPR**) elicits Ca2+ release in airway smooth muscle (ASM) cells through ryanodine receptor channels. CD38 is a cell surface protein that catalyzes the synthesis and degradation of **cADPR**. In inflammatory diseases such as **asthma**, augmented Ca2+ responses and Ca2+ sensitivity contribute to increased ASM contractility in response to agonists. In this study, we investigated the regulation of CD38 expression and the role of **cADPR**-mediated Ca2+ release in airway inflammation. Human ASM cells in culture between the second and fifth passages were exposed to tumor necrosis factor α (TNF-α), interleukin 1β, or interferon γ, or bovine serum albumin (controls). CD38 expression was measured by reverse transcriptase-polymerase chain reaction (RT-PCR), real-time PCR, and Western blot anal., and ADP-ribosyl cyclase activity was assayed with nicotinamide guanine dinucleotide as the substrate. Ca2+ responses to acetylcholine, bradykinin, and thrombin were measured in fura-2AM-loaded cells by fluorescence microscopy. Cytokines caused significant augmentation of CD38 expression, ADP-ribosyl cyclase activity, and Ca2+ responses to the agonists, compared with the control. TNF-α effects were greater than those of the other two cytokines. The **cADPR** antagonist 8-bromo-**cADPR** attenuated the Ca2+ responses to the agonists in control and cytokine-treated cells, with the magnitude of inhibition correlating with the level of CD38. This study provides the first demonstration of a role for CD38-**cADPR** signaling in a model of inflammatory airway disease.
REFERENCE COUNT: 65 THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 12 MEDLINE on STN
ACCESSION NUMBER: 2006007782 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16280365
TITLE: IL-4 inhibits calcium transients in bovine trachealis cells by a ryanodine receptor-dependent mechanism.
AUTHOR: Ethier Michael F; Madison J Mark
CORPORATE SOURCE: Department of Medicine, University of Massachusetts Medical School, Worcester, Massachusetts 01605, USA.
CONTRACT NUMBER: HL-54143 (NHLBI)
SOURCE: The FASEB journal : official publication of the Federation of American Societies for Experimental Biology, (2006 Jan) Vol. 20, No. 1, pp. 154-6. Electronic Publication: 2005-11-09.
Journal code: 8804484. E-ISSN: 1530-6860.
PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200603
ENTRY DATE: Entered STN: 6 Jan 2006
Last Updated on STN: 24 Mar 2006
Entered Medline: 23 Mar 2006

AB IL-4 and IL-13 have important roles in the pathogenesis of **asthma**. A novel finding was that brief exposure of airway smooth muscle cells to IL-4 inhibited carbachol-stimulated calcium transients. We hypothesized that IL-4 inhibits transients by decreasing calcium store content and tested this by measuring the effects of IL-4 on transients induced by a nonspecific ionophore. Bovine trachealis cells were loaded with fura 2-AM, and cytosolic calcium concentrations ([Ca2+]i) were measured in single cells by digital microscopy. Stimulation (S1) with carbachol (10 microM) caused rapid, transient increases in [Ca2+]i to 1299 +/- 355 nM (n=5). After recovery of calcium stores, stimulation (S2) of the same cells with ionomycin (10 microM), in the absence of extracellular calcium, also increased [Ca2+]i to give S2/S1 ratio of 1.03 +/- 0.29. However, after 20 min of IL-4 (50 ng/ml), but not IL-13, ionomycin transients were decreased to 0.50 +/- 0.16 (S2/S1, P=0.02, n=6). IL-4 did not inhibit transients with ryanodine receptor calcium release channels (RyR) blocked by ryanodine (200 microM) (S2/S1=1.01+/-0.11) but still did in the presence of 8-bromo cyclic ADP-ribose, an antagonist of cyclic ADP-ribose (**cADPR**) signaling at RyR (S2/S1=0.48+/-0.13). Together, findings suggest that IL-4 decreases intracellular calcium stores by mechanisms dependent on RyR, but not on **cADPR** signaling.

L4 ANSWER 8 OF 12 MEDLINE on STN
ACCESSION NUMBER: 2005186502 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15821018
TITLE: CD38/cyclic ADP-ribose signaling: role in the regulation of calcium homeostasis in airway smooth muscle.
AUTHOR: Deshpande Deepak A; White Thomas A; Dogan Soner; Walseth Timothy F; Panettieri Reynold A; Kannan Mathur S
CORPORATE SOURCE: Dept. of Veterinary and Biomedical Sciences, University of Minnesota, St. Paul, MN 55108, USA.
CONTRACT NUMBER: DA-11806 (NIDA)
HL-057498 (NHLBI)
HL-55301 (NHLBI)
HL-64063 (NHLBI)
SOURCE: American journal of physiology. Lung cellular and molecular physiology, (2005 May) Vol. 288, No. 5, pp. L773-88. Ref: 178
Journal code: 100901229. ISSN: 1040-0605.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200505
ENTRY DATE: Entered STN: 12 Apr 2005
Last Updated on STN: 17 May 2005
Entered Medline: 16 May 2005

AB The contractility of airway smooth muscle cells is dependent on dynamic changes in the concentration of intracellular calcium. Signaling molecules such as inositol 1,4,5-trisphosphate and cyclic ADP-ribose play pivotal roles in the control of intracellular calcium concentration. Alterations in the processes involved in the regulation of intracellular calcium concentration contribute to the pathogenesis of airway diseases such as **asthma**. Recent studies have identified cyclic ADP-ribose as a calcium-mobilizing second messenger in airway smooth muscle cells, and modulation of the pathway involved in its metabolism

results in altered calcium homeostasis and may contribute to airway hyperresponsiveness. In this review, we describe the basic mechanisms underlying the dynamics of calcium regulation and the role of CD38/**cADPR**, a novel pathway, in the context of airway smooth muscle function and its contribution to airway diseases such as **asthma**.

L4 ANSWER 9 OF 12 MEDLINE on STN
ACCESSION NUMBER: 2004383527 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15266023
TITLE: Tumor necrosis factor-alpha differentially regulates the expression of proinflammatory genes in human airway smooth muscle cells by activation of interferon-beta-dependent CD38 pathway.
AUTHOR: Tliba Omar; Panettieri Reynold A Jr; Tliba Samira; Walseth Timothy F; Amrani Yassine
CORPORATE SOURCE: Pulmonary, Allergy, and Critical Care Division, Department of Medicine, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania 19104-6160, USA.
CONTRACT NUMBER: 2R01-HL55301 (NHLBI)
DA11806 (NIDA)
HL67663 (NHLBI)
SOURCE: Molecular pharmacology, (2004 Aug) Vol. 66, No. 2, pp. 322-9.
Journal code: 0035623. ISSN: 0026-895X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200408
ENTRY DATE: Entered STN: 4 Aug 2004
Last Updated on STN: 31 Aug 2004
Entered Medline: 30 Aug 2004

AB Recent evidence suggests that CD38, an ectoenzyme that converts NAD(+) to cyclic ADP-ribose (**cADPr**), may play a role in cytokine-induced airway smooth muscle (ASM) cell hyper-responsiveness, a key feature associated with chronic **asthma**. In the present study, we investigated the major signaling pathways by which tumor necrosis factor-alpha (TNFalpha) induces CD38 expression and its role in regulating gene expression in human ASM cells. Using flow cytometry analyses, TNFalpha enhanced CD38 expression in a manner that was time-(0-24 h), concentration-(0.1-40 ng/ml), and protein synthesis-(cycloheximide blockade) dependent. A selective agonistic antibody against tumor necrosis factor receptor (TNFR) 1 also augmented CD38 expression, whereas anti-TNFR2 antagonistic antibody did not prevent the TNFalpha response. Inhibition of the Janus activated kinase/signal transducer and activator of transcription pathways using the soluble inhibitor 2-(1,1-dimethylethyl)-9-fluoro-3,6-dihydro-7H-benz-[h]imidaz[4,5-f]isoquinolin-7-one (DBI) or with neutralizing antibody against interferon beta (IFNbeta) completely abrogated TNFalpha-induced CD38 expression at both protein and mRNA levels. Combining TNFalpha (0.1 and 1 ng/ml) and IFNbeta (100 IU/ml) at concentrations alone that had little effect on CD38 expression induced a robust synergistic induction of CD38 mRNA and protein levels. 8-Bromo-**cADPr**, a **cADPr** antagonist, significantly augmented TNFalpha-induced interleukin-6 secretion, whereas regulated on activation normal T cell expressed and secreted secretion was suppressed. 8-Bromo-**cADPr**, however, did not affect TNFalpha-induced cell surface expression of intercellular adhesion molecule-1. Our study is the first to demonstrate that IFNbeta-dependent activation of CD38 pathway is a novel component by which TNFalpha differentially regulates the expression of inflammatory genes in ASM cells.

L4 ANSWER 10 OF 12 MEDLINE on STN
ACCESSION NUMBER: 2004304788 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14764428

TITLE: Modulation of calcium signaling by interleukin-13 in human airway smooth muscle: role of CD38/cyclic adenosine diphosphate ribose pathway.
AUTHOR: Deshpande Deepak A; Dogan Soner; Walseth Timothy F; Miller Steven M; Amrani Yassine; Panettieri Reynold A; Kannan Mathur S
CORPORATE SOURCE: Department of Veterinary PathoBiology, University of Minnesota, St. Paul, MN, USA.
CONTRACT NUMBER: DA11806 (NIDA)
HL057498 (NHLBI)
HL55301 (NHLBI)
HL64063 (NHLBI)
SOURCE: American journal of respiratory cell and molecular biology, (2004 Jul) Vol. 31, No. 1, pp. 36-42. Electronic Publication: 2004-02-05.
Journal code: 8917225. ISSN: 1044-1549.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200408
ENTRY DATE: Entered STN: 24 Jun 2004
Last Updated on STN: 25 Aug 2004
Entered Medline: 24 Aug 2004

AB CD38/cyclic adenosine diphosphate ribose (**cADPR**) signaling plays an important role in the regulation of intracellular calcium responses to agonists in a variety of cells, including airway smooth muscle (ASM) cells. The present study was aimed at determining the effect of interleukin (IL)-13, a cytokine implicated in the pathogenesis of **asthma**, on CD38/**cADPR** signaling and to ascertain the contribution of CD38/**cADPR** signaling to IL-13-induced airway hyperresponsiveness. Human ASM cells maintained in culture were exposed to 50 ng/ml IL-13 for 22 h and levels of CD38 expression and intracellular calcium responses to agonists were measured. Treatment of human ASM cells with IL-13 resulted in increased CD38 expression as determined by real-time polymerase chain reaction, Western blot analysis, and indirect immunofluorescence. Increased CD38 expression was reflected as increased ADP-ribosyl cyclase activity in the ASM cell membranes. The net intracellular calcium responses to bradykinin, thrombin, and histamine were significantly ($P < or = 0.05$) higher in cells treated with IL-13 compared with controls. Furthermore, 8-bromo-**cADPR**, a **cADPR** antagonist, attenuated IL-13-induced augmented intracellular calcium responses to agonists in human ASM cells. These findings indicate that the CD38/**cADPR**-dependent pathway has a major role in IL-13-induced modulation of calcium signaling in human ASM.

L4 ANSWER 11 OF 12 MEDLINE on STN
ACCESSION NUMBER: 2004241782 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15140413
TITLE: Bronchial hyperresponsiveness: insights into new signaling molecules.
AUTHOR: Amrani Yassine; Tliba Omar; Deshpande Deepak A; Walseth Timothy F; Kannan Mathur S; Panettieri Reynold A Jr
CORPORATE SOURCE: Pulmonary, Allergy and Critical Care Division, Department of Medicine, University of Pennsylvania Medical Center, BRB II/III, 421 Curie Boulevard, Philadelphia, PA 19104, USA.. amrani@mail.med.upenn.edu
CONTRACT NUMBER: 1P50 HL 67663 (NHLBI)
2R01 HL 55301 (NHLBI)
2R01 HL 57498 (NHLBI)
DA 11806 (NIDA)
SOURCE: Current opinion in pharmacology, (2004 Jun) Vol. 4, No. 3, pp. 230-4. Ref: 44
Journal code: 100966133. ISSN: 1471-4892.

PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200409
ENTRY DATE: Entered STN: 14 May 2004
Last Updated on STN: 15 Sep 2004
Entered Medline: 14 Sep 2004

AB Signaling molecules play a critical role in the pathophysiology of airway diseases. Recent evidence shows that cyclic ADP-ribose (**cADPr**), an endogenous activator of the ryanodine receptor channel in mammalian cells, modulates agonist-induced calcium responses in airway smooth muscle (ASM) cells. In addition, **cADPr**-mediated calcium release appears to play an important role in the "non-specific" increased ASM responsiveness to contractile agonists in cytokine-treated cells, a characteristic finding of **asthma**. Furthermore, other signaling molecules such as Rho/Rho kinase and phosphodiesterase also contribute to bronchial hyperresponsiveness. Thus, a better understanding of these signaling molecules that alter calcium signaling and contractility of ASM might provide new insight into novel therapeutic targets for the control of bronchial hyperresponsiveness.

L4 ANSWER 12 OF 12 MEDLINE on STN
ACCESSION NUMBER: 2003118202 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12514117
TITLE: CD38/cyclic ADP-ribose-mediated Ca2+ signaling contributes to airway smooth muscle hyper-responsiveness.
AUTHOR: Deshpande Deepak A; Walseth Timothy F; Panettieri Reynold A; Kannan Mathur S
CORPORATE SOURCE: Department of Veterinary PathoBiology, University of Minnesota, St. Paul, Minnesota 55108, USA.
SOURCE: The FASEB journal : official publication of the Federation of American Societies for Experimental Biology, (2003 Mar) Vol. 17, No. 3, pp. 452-4. Electronic Publication: 2003-01-02.
Journal code: 8804484. E-ISSN: 1530-6860.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200304
ENTRY DATE: Entered STN: 13 Mar 2003
Last Updated on STN: 2 Apr 2003
Entered Medline: 1 Apr 2003

AB We previously demonstrated that cyclic ADP-ribose (**cADPR**) elicits Ca2+ release in airway smooth muscle (ASM) cells through ryanodine receptor channels. CD38 is a cell surface protein that catalyzes the synthesis and degradation of **cADPR**. In inflammatory diseases such as **asthma**, augmented Ca2+ responses and Ca2+ sensitivity contribute to increased ASM contractility in response to agonists. In this study, we investigated the regulation of CD38 expression and the role of **cADPR**-mediated Ca2+ release in airway inflammation. Human ASM cells in culture between the second and fifth passages were exposed to tumor necrosis factor alpha (TNF-alpha), interleukin 1beta, or interferon gamma, or bovine serum albumin (controls). CD38 expression was measured by reverse transcriptase-polymerase chain reaction (RT-PCR), real-time PCR, and Western blot analysis, and ADP-ribosyl cyclase activity was assayed with nicotinamide guanine dinucleotide as the substrate. Ca2+ responses to acetylcholine, bradykinin, and thrombin were measured in fura-2AM-loaded cells by fluorescence microscopy. Cytokines caused significant augmentation of CD38 expression, ADP-ribosyl cyclase activity, and Ca2+ responses to the agonists, compared with the control. TNF-alpha effects were greater than those of the other two cytokines. The

cADPR antagonist 8-bromo-**cADPR** attenuated the Ca2+ responses to the agonists in control and cytokine-treated cells, with the magnitude of inhibition correlating with the level of CD38. This study provides the first demonstration of a role for CD38-**cADPR** signaling in a model of inflammatory airway disease.

L5 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:259650 CAPLUS
DOCUMENT NUMBER: 142:291376
TITLE: Extracellular NAD+ and cyclic adenosine diphosphate ribose (cADPR) as potent antiinflammatory agents
INVENTOR(S): Fink, Mitchell P.; Delude, Russell L.; Han, Xianonan
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 18 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005065109	A1	20050324	US 2003-659063	20030910
PRIORITY APPLN. INFO.:			US 2003-659063	20030910

AB A method of prophylaxis or treatment of inflammatory conditions, including, but not limited to, intestinal epithelial inflammation due to intestine-specific conditions (e.g., Crohn's disease or ulcerative colitis) or systemic causes of inflammation (e.g., endotoxemia, **sepsis**, hemorrhagic shock/resuscitation or pancreatitis) is disclosed. In the method, an affected patient is administered a therapeutically effective amount of a composition including an NAD-related compound, in a form that is accessible to a receptor mol., conveyed in a pharmaceutically acceptable carrier vehicle. NAD-related compds. include NAD (NAD+), cyclic ADP ribose (**cADPR**), or functionally equivalent analogs, derivs., metabolites or agonists thereof, or prodrugs therefor. Also disclosed are ex vivo and in vivo assay methods to test candidate compds. for activity, kits for carrying out the therapeutic methods or the assay methods of the invention and articles of manufacture that include compns. for use in the methods of the invention and instructions for the use thereof.

L17 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:259650 CAPLUS
DOCUMENT NUMBER: 142:291376
TITLE: Extracellular NAD+ and cyclic adenosine diphosphate ribose (cADPR) as potent antiinflammatory agents
INVENTOR(S): Fink, Mitchell P.; Delude, Russell L.; Han, Xianonan
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 18 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005065109	A1	20050324	US 2003-659063	20030910
PRIORITY APPLN. INFO.:			US 2003-659063	20030910

AB A method of prophylaxis or treatment of inflammatory conditions, including, but not limited to, intestinal epithelial inflammation due to intestine-specific conditions (e.g., Crohn's **disease** or ulcerative colitis) or systemic causes of inflammation (e.g., endotoxemia, sepsis, hemorrhagic shock/resuscitation or pancreatitis) is disclosed. In the method, an affected patient is administered a therapeutically effective amount of a composition including an NAD-related compound, in a form that is accessible to a receptor mol., conveyed in a pharmaceutically acceptable carrier vehicle. NAD-related compds. include NAD (NAD+), cyclic ADP ribose (**cADPR**), or functionally equivalent **analogs**, derivs., metabolites or agonists thereof, or prodrugs therefor. Also disclosed are ex vivo and in vivo assay methods to test candidate compds. for activity, kits for carrying out the therapeutic methods or the assay methods of the invention and articles of manufacture that include compns. for use in the methods of the invention and instructions for the use thereof.

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L17 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:259650 CAPLUS
DOCUMENT NUMBER: 142:291376
TITLE: Extracellular NAD+ and cyclic adenosine diphosphate ribose (cADPR) as potent antiinflammatory agents
INVENTOR(S): Fink, Mitchell P.; Delude, Russell L.; Han, Xianonan
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 18 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005065109	A1	20050324	US 2003-659063	20030910
PRIORITY APPLN. INFO.:			US 2003-659063	20030910

AB A method of prophylaxis or treatment of inflammatory conditions, including, but not limited to, intestinal epithelial inflammation due to intestine-specific conditions (e.g., Crohn's **disease** or ulcerative colitis) or systemic causes of inflammation (e.g., endotoxemia, sepsis, hemorrhagic shock/resuscitation or pancreatitis) is disclosed. In the method, an affected patient is administered a therapeutically

effective amount of a composition including an NAD-related compound, in a form that is accessible to a receptor mol., conveyed in a pharmaceutically acceptable carrier vehicle. NAD-related compds. include NAD (NAD+), cyclic ADP ribose (**cADPR**), or functionally equivalent **analogs**, derivs., metabolites or agonists thereof, or prodrugs therefor. Also disclosed are ex vivo and in vivo assay methods to test candidate compds. for activity, kits for carrying out the therapeutic methods or the assay methods of the invention and articles of manufacture that include compns. for use in the methods of the invention and instructions for the use thereof.

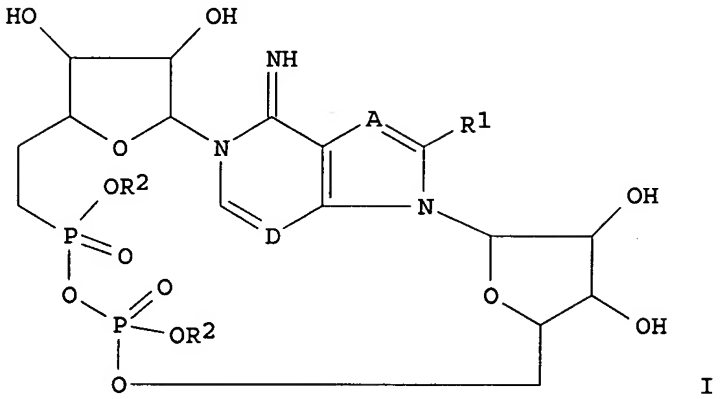
L17 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:93934 CAPLUS
DOCUMENT NUMBER: 140:162333
TITLE: Chemotaxis and calcium responses of phagocytes to formyl peptide receptor ligands is differentially regulated by cyclic ADP ribose
AUTHOR(S): Partida-Sanchez, Santiago; Iribarren, Pablo; Moreno-Garcia, Miguel E.; Gao, Ji-Liang; Murphy, Philip M.; Oppenheimer, Norman; Wang, Ji Ming; Lund, Frances E.
CORPORATE SOURCE: Trudeau Institute, Saranac Lake, NY, 12983, USA
SOURCE: Journal of Immunology (2004), 172(3), 1896-1906
CODEN: JOIMA3; ISSN: 0022-1767
PUBLISHER: American Association of Immunologists
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Cyclic ADP ribose (**cADPR**) is a calcium-mobilizing metabolite that regulates intracellular calcium release and extracellular calcium influx. Although the role of **cADPR** in modulating calcium mobilization has been extensively examined, its potential role in regulating immunol. responses is less well understood. The authors previously reported that **cADPR**, produced by the ADP-ribosyl cyclase, CD38, controls calcium influx and chemotaxis of murine neutrophils responding to fMLF, a peptide agonist for two chemoattractant receptor subtypes, formyl peptide receptor and formyl peptide receptor-like 1. Here, they examine whether **cADPR** is required for chemotaxis of human monocytes and neutrophils to a diverse array of chemoattractants. They found that a **cADPR** antagonist and a CD38 substrate **analog** inhibited the chemotaxis of human phagocytic cells to a number of formyl peptide receptor-like 1-specific ligands but had no effect on the chemotactic response of these cells to ligands selective for formyl peptide receptor. In addition, the authors show that the **cADPR** antagonist blocks the chemotaxis of human monocytes to CXCR4, CCR1, and CCR5 ligands. In all cases, the authors found that **cADPR** modulates intracellular free calcium levels in cells activated by chemokines that induce extracellular calcium influx in the apparent absence of intracellular calcium release. Thus, **cADPR** regulates calcium signaling of a discrete subset of chemoattractant receptors expressed by human leukocytes. Since many of the chemoattractant receptors regulated by **cADPR** bind to ligands that are associated with clin. pathol., **cADPR** and CD38 represent novel drug targets with potential application in chronic inflammatory and neurodegenerative **disease**.
REFERENCE COUNT: 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:545762 CAPLUS
DOCUMENT NUMBER: 139:95491
TITLE: Cyclic-ADP-ribose analogs
INVENTOR(S): Walseth, Timothy F.; De Flora, Antonio; Zocchi, Elena; Podesta, Marina; Wong, Long; Aarhus, Robert A.; Lee, Hon Cheung

PATENT ASSIGNEE(S): Regents of the University of Minnesota, USA
SOURCE: U.S., 22 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6593307	B1	20030715	US 2000-698611	20001027
PRIORITY APPLN. INFO.:			US 1999-161820P P	19991027

OTHER SOURCE(S): MARPAT 139:95491
GI



I

AB The present invention provides compds. and methods that are useful for promoting the proliferation of hemopoietic progenitor cells without cell differentiation. Accordingly, the invention provides a compound of formula I wherein: A is -N= or -C(H)=; D is -C(H)=; R1 is hydrogen, amino, azido, or halo; and each R2 is independently hydrogen, or a suitable photolabile caging group; or a salt or a detectably labeled derivative thereof. Certain compds. of formula I (e.g. compds. wherein R1 is hydrogen) may be particularly useful to mobilize intracellular calcium. Other compds. of the invention (e.g. compds. wherein R1 is amino, azido or halo) may be particularly as stable antagonists of cADPR (cyclic-ADP-ribose) and cADPR induced calcium release. The invention also provides a method to promote the proliferation of a lymphocyte and to enhance the immune system of a mammal comprising administering to a mammal in need of such treatment, an amount of a compound of formula I or a salt thereof.

REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 4 OF 4 MEDLINE on STN
ACCESSION NUMBER: 2004047399 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14734775
TITLE: Chemotaxis and calcium responses of phagocytes to formyl peptide receptor ligands is differentially regulated by cyclic ADP ribose.
AUTHOR: Partida-Sanchez Santiago; Iribarren Pablo; Moreno-Garcia Miguel E; Gao Ji-Liang; Murphy Philip M; Oppenheimer Norman; Wang Ji Ming; Lund Frances E
CORPORATE SOURCE: Trudeau Institute, Saranac Lake, NY 12983, USA.
SOURCE: Journal of immunology (Baltimore, Md. : 1950), (2004 Feb 1) Vol. 172, No. 3, pp. 1896-906.

Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200405
ENTRY DATE: Entered STN: 30 Jan 2004
Last Updated on STN: 10 May 2004
Entered Medline: 7 May 2004

AB Cyclic ADP ribose (**cADPR**) is a calcium-mobilizing metabolite that regulates intracellular calcium release and extracellular calcium influx. Although the role of **cADPR** in modulating calcium mobilization has been extensively examined, its potential role in regulating immunologic responses is less well understood. We previously reported that **cADPR**, produced by the ADP-ribosyl cyclase, CD38, controls calcium influx and chemotaxis of murine neutrophils responding to fMLF, a peptide agonist for two chemoattractant receptor subtypes, formyl peptide receptor and formyl peptide receptor-like 1. In this study, we examine whether **cADPR** is required for chemotaxis of human monocytes and neutrophils to a diverse array of chemoattractants. We found that a **cADPR** antagonist and a CD38 substrate **analogue** inhibited the chemotaxis of human phagocytic cells to a number of formyl peptide receptor-like 1-specific ligands but had no effect on the chemotactic response of these cells to ligands selective for formyl peptide receptor. In addition, we show that the **cADPR** antagonist blocks the chemotaxis of human monocytes to CXCR4, CCR1, and CCR5 ligands. In all cases, we found that **cADPR** modulates intracellular free calcium levels in cells activated by chemokines that induce extracellular calcium influx in the apparent absence of significant intracellular calcium release. Thus, **cADPR** regulates calcium signaling of a discrete subset of chemoattractant receptors expressed by human leukocytes. Since many of the chemoattractant receptors regulated by **cADPR** bind to ligands that are associated with clinical pathology, **cADPR** and CD38 represent novel drug targets with potential application in chronic inflammatory and neurodegenerative **disease**.

L18 ANSWER 13 OF 16 MEDLINE on STN
ACCESSION NUMBER: 2000033422 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10564770
TITLE: Cyclic 3-deaza-adenosine diphosphoribose: a potent and stable analog of cyclic ADP-ribose.
AUTHOR: Wong L; Aarhus R; Lee H C; Walseth T F
CORPORATE SOURCE: Department of Pharmacology, University of Minnesota Medical School, Minneapolis, MN 55455, USA.
CONTRACT NUMBER: DA11806 (NIDA)
HD17484 (NICHD)
SOURCE: Biochimica et biophysica acta, (1999 Nov 16) Vol. 1472, No. 3, pp. 555-64.
Journal code: 0217513. ISSN: 0006-3002.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 14 Jan 2000
Last Updated on STN: 14 Jan 2000
Entered Medline: 6 Jan 2000

AB Cyclic 3-deaza-adenosine diphosphoribose (3-deaza-**cADPR**), an **analog** of cyclic adenosine diphosphoribose (**cADPR**) was synthesized. 3-deaza-**cADPR** differs from **cADPR** by only the substitution of carbon for nitrogen at the 3-position of the purine ring. Similar to **cADPR**, the **analog** has potent calcium releasing activity in sea urchin egg homogenates and was able to induce calcium release at concentrations as low as 0.3 nM. The EC(50) value for 3-deaza-**cADPR**-induced calcium release was 1 nM, which is about 70 times more potent than **cADPR**. The properties of calcium release induced by 3-deaza-**cADPR** in all other respects were similar to those of **cADPR**. Thus, 3-deaza-**cADPR** and **cADPR** were capable of cross-desensitizing each other and their calcium releasing activities were potentiated by Sr(2+) as well as caffeine. 8-amino-**cADPR**, a selective antagonist of **cADPR** , was also able to inhibit 3-deaza-**cADPR** induced calcium release. Taken together, these data suggest that 3-deaza-**cADPR** releases calcium through the same mechanism as **cADPR**. 3-deaza-**cADPR** was found to be resistant to both heat and enzymatic hydrolysis. Only 15% of 3-deaza-**cADPR** was destroyed after boiling this compound for 2 h. No loss of 3-deaza-**cADPR** was observed when treated with CD38 under **conditions** where **cADPR** was completely hydrolyzed. Thus, 3-deaza-**cADPR** is a potent and stable **analog** of **cADPR**. These properties should make 3-deaza-**cADPR** a useful probe in studies focused on the mechanism of **cADPR** action.

L18 ANSWER 8 OF 16 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:708280 CAPLUS
DOCUMENT NUMBER: 128:21051
TITLE: Actions of cADP-ribose and its antagonists on contraction in guinea pig isolated ventricular myocytes: influence of temperature
AUTHOR(S): Iino, Shigeo; Cui, Yi; Galione, Antony; Terrar, Derek A.
CORPORATE SOURCE: Department of Pharmacology, University of Oxford, Oxford, OX1 3QT, UK
SOURCE: Circulation Research (1997), 81(5), 879-884
CODEN: CIRUAL; ISSN: 0009-7330
PUBLISHER: American Heart Association
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Although it is becoming widely accepted that cADP-ribose (**cADPR**) can regulate calcium release from the endoplasmic reticulum in sea urchin eggs and in a variety of mammalian cell types, it remains controversial whether this substance might influence calcium release during excitation-contraction coupling in cardiac muscle. We have investigated possible actions of **cADPR** in intact cells isolated from guinea pig ventricle, paying particular attention to the possible influence of temperature At 36°C, myocyte contraction was influenced by cytosolic application of **cADPR** in a concentration-dependent manner (showing an ≈30% increase in contraction with 5 μmol/L **cADPR** applied via a patch pipet in myocytes stimulated to fire action potentials at 1 Hz). Calcium transients measured with fura 2 were also increased by 5 μmol/L **cADPR**. Antagonists of **cADPR** reduced contraction at 36°C (by ≈35% with either 50 μmol/L 8-Br-**cADPR** or 5 μmol/L 8-amino- **cADPR** applied via the patch pipet). At room temperature (≈20°C to 24°C), no significant effects on contraction were detected with either **cADPR** or its antagonists. At 36°C, treatment of the cells with a mixture of 2 μmol/L ryanodine and 1 μmol/L thapsigargin to suppress function of the sarcoplasmic reticulum stores of calcium prevented the action of 5 μmol/L **cADPR** applied via a patch pipet. These observations are consistent with an action of cytosolic **cADPR** to enhance calcium-induced calcium release from the sarcoplasmic reticulum in guinea pig ventricular myocytes at 36°C. The observed influence of temperature under the **conditions** of our expts. is one factor that might help to account for failure to detect actions of **cADPR** and its **analogs** in some previous studies.
REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 9 OF 16 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:185124 CAPLUS
DOCUMENT NUMBER: 126:251360
TITLE: Non-enzymic preparation of cyclic ADP-ribose via intramol. stereoselective cyclization of β-NAD.
INVENTOR(S): Sih, Charles J.
PATENT ASSIGNEE(S): Wisconsin Alumni Research Foundation, USA
SOURCE: U.S., 8 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5608047	A	19970304	US 1995-404467	19950315
PRIORITY APPLN. INFO.:			US 1995-404467	19950315

AB A non-enzymic stereoselective cyclization of β-NAD+ to yield cyclic ADP-ribose (**cADPR**). By heating β-NAD+ in an anhydrous solvent in the presence of a metal halide and a nonnucleophilic base, **cADPR** was obtained as the sole cyclic isomer in yields as high as 28%. α-NAD was also converted into **cADPR** under the same reaction **conditions**. Several **analogs** of **cADPR** have also been synthesized and some of these **analogs** have a greater Ca++ release activity than **cADPR** itself.

L18 ANSWER 10 OF 16 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:238064 CAPLUS
DOCUMENT NUMBER: 122:133647
TITLE: Regioselective ribosylation of the base residue of adenosine derivatives and its application to the synthesis of cyclic ADP-ribose
AUTHOR(S): Aritomo, Keiichi; Urashima, Chihiro; Wada, Takeshi; Sekine, Mitsuo
CORPORATE SOURCE: Dep. Life Sci., Tokyo Inst. Technol., Midoriku, 227, Japan
SOURCE: Nucleic Acids Symposium Series (1994), 31(21st Symposium on Nucleic Acids Chemistry, 1994), 7-8
CODEN: NACSD8; ISSN: 0261-3166
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Phase transfer catalysis (PTC) was useful for regioselective and stereoselective ribosylation of adenosine derivs. and other purine nucleoside derivs. Under PTC **conditions**, 1,9-diribofuranosylpurine derivs. were synthesized as intermediates for the synthesis of cyclic ADP-ribose (**cADPR**) and its **analogs**
.

L18 ANSWER 11 OF 16 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:178132 CAPLUS
DOCUMENT NUMBER: 122:10454
TITLE: Cyclic ADP-Ribose via Stereoselective Cyclization of β-NAD
AUTHOR(S): Yamada, Shinji; Gu, Qu-Ming; Sih, Charles J.
CORPORATE SOURCE: School of Pharmacy, University of Wisconsin, Madison, WI, 53706, USA
SOURCE: Journal of the American Chemical Society (1994), 116(23), 10787-8
CODEN: JACSAT; ISSN: 0002-7863
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 122:10454
AB A non-enzymic stereoselective cyclization of β-NAD+ to yield cyclic ADP-ribose (**cADPR**) has been achieved. By reacting β-NAD+ with NaBr and triethylamine in dry DMSO at 70°, **cADPR** was obtained as the sole cyclic isomer in yields as high as 28%. Nicotinamide and this side product, ADP-ribose, were readily separated from **cADPR** by HPLC. This intramol. cyclization appeared to proceed via the formation of an oxocarbenium ion intermediate, for α-NAD was also converted into **cADPR** under the same reaction **conditions**. Several **analogs** of **cADPR** have been prepared to illustrate the versatility of this method.

L18 ANSWER 12 OF 16 MEDLINE on STN
ACCESSION NUMBER: 2001468958 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11513738
TITLE: Kinetic competence of the cADP-ribose-CD38 complex as an intermediate in the CD38/NAD+ glycohydrolase-catalysed reactions: implication for CD38 signalling.
AUTHOR: Cakir-Kiefer C; Muller-Steffner H; Oppenheimer N; Schuber F

CORPORATE SOURCE: Laboratoire de Chimie Bioorganique, UMR 7514 CNRS-ULP, Faculte de Pharmacie, 74 route du Rhin, 67400 Strasbourg-Illkirch, France.
SOURCE: The Biochemical journal, (2001 Sep 1) Vol. 358, No. Pt 2, pp. 399-406.
Journal code: 2984726R. ISSN: 0264-6021.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200110
ENTRY DATE: Entered STN: 30 Aug 2001
Last Updated on STN: 18 Dec 2002
Entered Medline: 4 Oct 2001

AB CD38/NAD(+) glycohydrolase is a type II transmembrane glycoprotein widely used to study T- and B-cell activation and differentiation. CD38 is endowed with two different activities: it is a signal transduction molecule and an ectoenzyme that converts NAD(+) into ADP-ribose (NAD(+) glycohydrolase activity) and small proportions of cADP-ribose (**cADPR**; ADP-ribosyl cyclase activity), a calcium-mobilizing metabolite, which, ultimately, can also be hydrolysed (**cADPR** hydrolase activity). The relationship between these two properties, and strikingly the requirement for signalling in the formation of free or enzyme-complexed **cADPR**, is still ill-defined. In the present study we wanted to test whether the CD38-**cADPR** complex is kinetically competent in the conversion of NAD(+) into the reaction product ADP-ribose. In principle, such a complex could be invoked for cross-talk, via conformational changes, with neighbouring partner(s) of CD38 thus triggering the signalling phenomena. Analysis of the kinetic parameters measured for the CD38/NAD(+) glycohydrolase-catalysed hydrolysis of 2'-deoxy-2'-aminoribo-NAD(+) and ADP-cyclo[N1,C1']-2'-deoxy-2'-aminoribose (slowly hydrolysable **analogues** of NAD(+) and **cADPR** respectively) ruled out that the CD38-**cADPR** complex can accumulate under steady-state **conditions**. This was borne out by simulation of the prevalent kinetic mechanism of CD38, which involve the partitioning of a common E.ADP-ribosyl intermediate in the formation of the enzyme-catalysed reaction products. Using this mechanism, microscopic rate **conditions** were found which transform a NAD(+) glycohydrolase into an ADP-ribosyl cyclase. Altogether, the present work shows that if the cross-talk with a partner depends on a conformational change of CD38, this is most probably not attributable to the formation of the CD38-**cADPR** complex. In line with recent results on the conformational change triggered by CD38 ligands [Berthelier, Laboureau, Boulla, Schuber and Deterre (2000) Eur. J. Biochem. 267, 3056-3064], we believe that the Michaelis CD38-NAD(+) complex could play such a role instead.

L18 ANSWER 13 OF 16 MEDLINE on STN
ACCESSION NUMBER: 2000033422 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10564770
TITLE: Cyclic 3-deaza-adenosine diphosphoribose: a potent and stable analog of cyclic ADP-ribose.
AUTHOR: Wong L; Aarhus R; Lee H C; Walseth T F
CORPORATE SOURCE: Department of Pharmacology, University of Minnesota Medical School, Minneapolis, MN 55455, USA.
CONTRACT NUMBER: DA11806 (NIDA)
HD17484 (NICHD)
SOURCE: Biochimica et biophysica acta, (1999 Nov 16) Vol. 1472, No. 3, pp. 555-64.
Journal code: 0217513. ISSN: 0006-3002.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 14 Jan 2000
Last Updated on STN: 14 Jan 2000
Entered Medline: 6 Jan 2000

AB Cyclic 3-deaza-adenosine diphosphoribose (3-deaza-**cADPR**), an **analog** of cyclic adenosine diphosphoribose (**cADPR**) was synthesized. 3-deaza-**cADPR** differs from **cADPR** by only the substitution of carbon for nitrogen at the 3-position of the purine ring. Similar to **cADPR**, the **analog** has potent calcium releasing activity in sea urchin egg homogenates and was able to induce calcium release at concentrations as low as 0.3 nM. The EC(50) value for 3-deaza-**cADPR**-induced calcium release was 1 nM, which is about 70 times more potent than **cADPR**. The properties of calcium release induced by 3-deaza-**cADPR** in all other respects were similar to those of **cADPR**. Thus, 3-deaza-**cADPR** and **cADPR** were capable of cross-desensitizing each other and their calcium releasing activities were potentiated by Sr(2+) as well as caffeine. 8-amino-**cADPR**, a selective antagonist of **cADPR** , was also able to inhibit 3-deaza-**cADPR** induced calcium release. Taken together, these data suggest that 3-deaza-**cADPR** releases calcium through the same mechanism as **cADPR**. 3-deaza-**cADPR** was found to be resistant to both heat and enzymatic hydrolysis. Only 15% of 3-deaza-**cADPR** was destroyed after boiling this compound for 2 h. No loss of 3-deaza-**cADPR** was observed when treated with CD38 under **conditions** where **cADPR** was completely hydrolyzed. Thus, 3-deaza-**cADPR** is a potent and stable **analog** of **cADPR**. These properties should make 3-deaza-**cADPR** a useful probe in studies focused on the mechanism of **cADPR** action.

L18 ANSWER 14 OF 16 MEDLINE on STN
ACCESSION NUMBER: 1999168949 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10068448
TITLE: NADP+-Dependent internalization of recombinant CD38 in CHO cells.
AUTHOR: Chidambaram N; Chang C F
CORPORATE SOURCE: Faculty of Medicine, The National University of Singapore, Singapore, 119260.
SOURCE: Archives of biochemistry and biophysics, (1999 Mar 15) Vol. 363, No. 2, pp. 267-72.
Journal code: 0372430. ISSN: 0003-9861.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199905
ENTRY DATE: Entered STN: 25 May 1999
Last Updated on STN: 18 Dec 2002
Entered Medline: 13 May 1999

AB CD38 is a 46-kDa type II transmembrane glycoprotein that catalyses the synthesis of cyclic ADP-ribose (**cADPR**) from NAD+. **cADPR** is a second messenger known to regulate intracellular Ca2+-induced Ca2+-release (CICR). A recent study has revealed that CD38 in Namalwa B cells undergoes internalization upon exposure to external NAD+. In this study, recombinant rat CD38 was expressed in Chinese hamster ovary (CHO) cells and the possibility of the protein to undergo internalization upon exposure to a substrate **analog** NADP+ was examined. It was found that such treatment of CHO cells resulted in a decrease of ADP-ribosyl cyclase activity, as well as immunofluorescence of CD38 on the cell surface. The same treatment of CHO cells also resulted in intracellular clustering of CD38 molecules as revealed by confocal microscopic analysis. The internalized CD38 was purified using a streptavidin/biotin-based method and was found to exhibit both ADP-ribosyl cyclase and **cADPR** hydrolase activities. On immunoblot, the internalized CD38 appeared as a

monomer of 46 kDa under reducing **condition** of SDS-PAGE. Our data demonstrate that NADP+ can efficiently induce internalization of CD38, a process that may be important in the production of **cADPR** intracellularly to regulate CICR.

L18 ANSWER 15 OF 16 MEDLINE on STN
ACCESSION NUMBER: 1998016433 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9354813
TITLE: Mechanisms of calcium signaling by cyclic ADP-ribose and NAADP.
AUTHOR: Lee H C
CORPORATE SOURCE: Department of Physiology, University of Minnesota, Minneapolis, USA.
CONTRACT NUMBER: HD-17484 (NICHD)
HD-32040 (NICHD)
SOURCE: Physiological reviews, (1997 Oct) Vol. 77, No. 4, pp. 1133-64. Ref: 188
Journal code: 0231714. ISSN: 0031-9333.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199712
ENTRY DATE: Entered STN: 9 Jan 1998
Last Updated on STN: 18 Dec 2002
Entered Medline: 10 Dec 1997

AB Cells possess various mechanisms for transducing external signals to intracellular responses. The discovery of inositol 1,4,5-trisphosphate (IP3) as a messenger for mobilizing internal Ca2+ stores has centralized Ca2+ mobilization among signaling mechanisms. Results reviewed in this article establish that, in addition to IP3, the internal Ca2+ stores can be mobilized by at least two other molecules, cyclic ADP-ribose (**cADPR**) and nicotinic acid adenine dinucleotide phosphate (NAADP), via totally independent mechanisms. Cyclic ADP-ribose is a newly discovered cyclic nucleotide derived from NAD, but, unlike adenosine 3',5'-cyclic monophosphate, its main signaling function is modulation of Ca(2+)-induced Ca2+ release, a major mechanism of Ca2+ mobilization in addition to the IP3 pathway. Evidence shows that **cADPR** may in fact be responsible for mediating the Ca(2+)-mobilizing activity of the gaseous messenger nitric oxide. Cells responsive to **cADPR** are widespread and include species from plant to mammal, indicating the generality of **cADPR** as a signaling molecule. In addition to **cADPR**, NAADP, a metabolite of NADP, can also mobilize Ca2+ stores. The release mechanism and the stores on which NAADP acts are distinct from **cADPR** and IP3. Nicotinic acid adenine dinucleotide phosphate may play a role in generating Ca2+ oscillations, since liberation of NAADP in live cells by photolyzing its caged **analog** produces long lasting Ca2+ oscillations. These two new Ca2+ agonists are intimately related, since the same metabolic enzymes can, under appropriate **conditions** , synthesize either one, suggesting a unified mechanism may regulate both pathways. Elucidation of these two new Ca2+ mobilization pathways is likely to have an important impact on our understanding of cellular signaling mechanisms.

L18 ANSWER 16 OF 16 MEDLINE on STN
ACCESSION NUMBER: 1998012816 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9351463
TITLE: Actions of cADP-ribose and its antagonists on contraction in guinea pig isolated ventricular myocytes. Influence of temperature.
AUTHOR: Iino S; Cui Y; Galione A; Terrar D A
CORPORATE SOURCE: Department of Pharmacology, University of Oxford, U.K.

SOURCE: Circulation research, (1997 Nov) Vol. 81, No. 5, pp. 879-84.
Journal code: 0047103. ISSN: 0009-7330.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199712
ENTRY DATE: Entered STN: 9 Jan 1998
Last Updated on STN: 9 Jan 1998
Entered Medline: 2 Dec 1997

AB Although it is becoming widely accepted that cADP-ribose (**cADPR**) can regulate calcium release from the endoplasmic reticulum in sea urchin eggs and in a variety of mammalian cell types, it remains controversial whether this substance might influence calcium release during excitation-contraction coupling in cardiac muscle. We have investigated possible actions of **cADPR** in intact cells isolated from guinea pig ventricle, paying particular attention to the possible influence of temperature. At 36 degrees C, myocyte contraction was influenced by cytosolic application of **cADPR** in a concentration-dependent manner (showing an approximately 30% increase in contraction with 5 mumol/L **cADPR** applied via a patch pipette in myocytes stimulated to fire action potentials at 1 Hz). Calcium transients measured with fura 2 were also increased by 5 mumol/L **cADPR**. Antagonists of **cADPR** reduced contraction at 36 degrees C (by approximately 35% with either 50 mumol/L 8-Br-**cADPR** or 5 mumol/L 8-amino-**cADPR** applied via the patch pipette). At room temperature (approximately 20 degrees C to 24 degrees C), no significant effects on contraction were detected with either **cADPR** or its antagonists. At 36 degrees C, treatment of the cells with a mixture of 2 mumol/L ryanodine and 1 mumol/L thapsigargin to suppress function of the sarcoplasmic reticulum stores of calcium prevented the action of 5 mumol/L **cADPR** applied via a patch pipette. These observations are consistent with an action of cytosolic **cADPR** to enhance calcium-induced calcium release from the sarcoplasmic reticulum in guinea pig ventricular myocytes at 36 degrees C. The observed influence of temperature under the **conditions** of our experiments is one factor that might help to account for failure to detect actions of **cADPR** and its **analogues** in some previous studies.

L18 ANSWER 1 OF 16 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:259650 CAPLUS
DOCUMENT NUMBER: 142:291376
TITLE: Extracellular NAD+ and cyclic adenosine diphosphate ribose (cADPR) as potent antiinflammatory agents
INVENTOR(S): Fink, Mitchell P.; Delude, Russell L.; Han, Xianonan
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 18 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005065109	A1	20050324	US 2003-659063	20030910

PRIORITY APPLN. INFO.: US 2003-659063 20030910
AB A method of prophylaxis or treatment of inflammatory **conditions**, including, but not limited to, intestinal epithelial inflammation due to intestine-specific **conditions** (e.g., Crohn's disease or ulcerative colitis) or systemic causes of inflammation (e.g., endotoxemia, sepsis, hemorrhagic shock/resuscitation or pancreatitis) is disclosed. In the method, an affected patient is administered a therapeutically effective amount of a composition including an NAD-related compound, in a form that is accessible to a receptor mol., conveyed in a pharmaceutically acceptable carrier vehicle. NAD-related compds. include NAD (NAD+), cyclic ADP ribose (**cADPR**), or functionally equivalent **analogs**, derivs., metabolites or agonists thereof, or prodrugs therefor. Also disclosed are ex vivo and in vivo assay methods to test candidate compds. for activity, kits for carrying out the therapeutic methods or the assay methods of the invention and articles of manufacture that include compns. for use in the methods of the invention and instructions for the use thereof.

L18 ANSWER 2 OF 16 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:573673 CAPLUS
DOCUMENT NUMBER: 140:59888
TITLE: The Preparation of Butyrylated NAD+ Type of Biological Molecules
AUTHOR(S): Hwang, Ki-Jun; Kim, Beom-Tae; Kim, Uh-Hyun
CORPORATE SOURCE: College of Natural Science, Department of Chemistry and Research Center of Bioactive Materials, Chonbuk National University, Jeonju, S. Korea
SOURCE: Synthetic Communications (2003), 33(16), 2803-2810
CODEN: SYNCAV; ISSN: 0039-7911
PUBLISHER: Marcel Dekker, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 140:59888
AB Butyrylated NAD+ and its fluorescent **analog**, 1,N6-etheno NAD+ are prepared in good yields by employing two-phase system, i.e., water and CH2Cl2 containing dimethyaminopyridine and excess butyric anhydride. The reaction **condition** for this reaction is so specific that several other acylating **conditions** attempted totally failed, and this developed methodol. will be conveniently utilized for the further study of cyclic ADP-ribose (**cADPR**).
REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 3 OF 16 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:2405 CAPLUS

DOCUMENT NUMBER: 136:310109
TITLE: Synthesis of a novel N-1 carbocyclic, N-9 butyl analogue of cyclic ADP ribose (cADPR)
AUTHOR(S): Galeone, Aldo; Mayol, Luciano; Oliviero, Giorgia; Piccialli, Gennaro; Varra, Michela
CORPORATE SOURCE: Dipartimento di Chimica delle Sostanze Naturali, Universita di Napoli 'Federico II', Naples, I-80131, Italy
SOURCE: Tetrahedron (2002), 58(2), 363-368
CODEN: TETRAB; ISSN: 0040-4020
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 136:310109

AB A new **analog** of **cADPR** was prepared through a synthetic pathway starting from 6-chloropurine which underwent two sequential alkylations at N-9 and N-1, with formation of the hydroxymethylcyclopentyl hypoxanthine intermediate. The successive bis-phosphorylation of hydroxyalkyl functions, followed by deprotection and reprotection steps, afforded the substrate for the cyclization reaction. This was carried out according to the Matsuda procedure and led to the intramol. pyrophosphate bond formation. The final deprotection in alkaline **conditions** gave the target compound in good yield.

REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 4 OF 16 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:691453 CAPLUS
DOCUMENT NUMBER: 136:2193
TITLE: Kinetic competence of the cADP-ribose-CD38 complex as an intermediate in the CD38/NAD+ glycohydrolase-catalysed reactions: implication for CD38 signalling
AUTHOR(S): Cakir-Kiefer, Celine; Muller-Steffner, Helene; Oppenheimer, Norman; Schuber, Francis
CORPORATE SOURCE: Laboratoire de Chimie Bioorganique, UMR 7514 CNRS-ULP, Faculte de Pharmacie, Strasbourg-Illkirch, 67400, Fr.
SOURCE: Biochemical Journal (2001), 358(2), 399-406
CODEN: BIJOAK; ISSN: 0264-6021
PUBLISHER: Portland Press Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 136:2193

AB CD38/NAD+ glycohydrolase is a type II transmembrane glycoprotein widely used to study T- and B-cell activation and differentiation. CD38 is endowed with two different activities: it is a signal transduction mol. and an ectoenzyme that converts NAD+ into ADP-ribose (NAD+ glycohydrolase activity) and small proportions of cADP-ribose (**cADPR**; ADP-ribosyl cyclase activity), a calcium-mobilizing metabolite, which, ultimately, can also be hydrolyzed (**cADPR** hydrolase activity). The relationship between these two properties, and strikingly the requirement for signaling in the formation of free or enzyme-complexed **cADPR**, is still ill-defined. In the present study we wanted to test whether the CD38-**cADPR** complex is kinetically competent in the conversion of NAD+ into the reaction product ADP-ribose. In principle, such a complex could be invoked for cross-talk, via conformational changes, with neighboring partner(s) of CD38 thus triggering the signaling phenomena. Anal. of the kinetic parameters measured for the CD38/NAD+ glycohydrolase-catalyzed hydrolysis of 2'-deoxy-2'-aminoribo-NAD+ and ADP-cyclo[N1,C1']-2'-deoxy-2'-aminoribose (slowly hydrolyzable **analogs** of NAD+ and **cADPR**, resp.) ruled out that the CD38-**cADPR** complex can accumulate under steady-state **conditions**. This was borne out by simulation of the prevalent kinetic mechanism of CD38, which involve the partitioning of a common E·ADP-ribosyl intermediate in the formation of the

enzyme-catalyzed reaction products. Using this mechanism, microscopic rate **conditions** were found which transform a NAD+ glycohydrolase into an ADP-ribosyl cyclase. Altogether, the present work shows that if the cross-talk with a partner depends on a conformational change of CD38, this is most probably not attributable to the formation of the CD38-**cADPR** complex. In line with recent results on the conformational change triggered by CD38 ligands, we believe that the Michaelis CD38 NAD+ complex could play such a role instead.

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 5 OF 16 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1999:734645 CAPLUS
DOCUMENT NUMBER: 132:73235
TITLE: Cyclic 3-deaza-adenosine diphosphoribose: a potent and stable analog of cyclic ADP-ribose
AUTHOR(S): Wong, L.; Aarhus, R.; Cheung Lee, H.; Walseth, T. F.
CORPORATE SOURCE: Department of Pharmacology, University of Minnesota Medical School, Minneapolis, MN, USA
SOURCE: Biochimica et Biophysica Acta, General Subjects (1999), 1472(3), 555-564
CODEN: BBGSB3; ISSN: 0304-4165
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Cyclic 3-deaza-adenosine diphosphoribose (3-deaza-**cADPR**), an **analog** of cyclic adenosine diphosphoribose (**cADPR**) was synthesized. 3-Deaza-**cADPR** differs from **cADPR** by only the substitution of carbon for nitrogen at the 3-position of the purine ring. Similar to **cADPR**, the **analog** has potent calcium releasing activity in sea urchin egg homogenates and was able to induce calcium release at concns. as low as 0.3 nM. The EC50 value for 3-deaza-**cADPR**-induced calcium release was 1 nM, which is about 70 times more potent than **cADPR**. The properties of calcium release induced by 3-deaza-**cADPR** in all other respects were similar to those of **cADPR**. Thus, 3-deaza-**cADPR** and **cADPR** were capable of cross-desensitizing each other and their calcium releasing activities were potentiated by Sr2+ as well as caffeine. 8-amino-**cADPR**, a selective antagonist of **cADPR**, was also able to inhibit 3-deaza-**cADPR** induced calcium release. Taken together, these data suggest that 3-deaza-**cADPR** releases calcium through the same mechanism as **cADPR**. 3-deaza-**cADPR** was found to be resistant to both heat and enzymic hydrolysis. Only 15% of 3-deaza-**cADPR** was destroyed after boiling this compound for 2 h. No loss of 3-deaza-**cADPR** was observed when treated with CD38 under **conditions** where **cADPR** was completely hydrolyzed. Thus, 3-deaza-**cADPR** is a potent and stable **analog** of **cADPR**. These properties should make 3-deaza-**cADPR** a useful probe in studies focused on the mechanism of **cADPR** action.

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 6 OF 16 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1999:152055 CAPLUS
DOCUMENT NUMBER: 131:3128
TITLE: NADP+-Dependent Internalization of Recombinant CD38 in CHO Cells
AUTHOR(S): Chidambaram, Natesavelalar; Chang, Chan Fong
CORPORATE SOURCE: Department of Biochemistry, Faculty of Medicine, The National University of Singapore, 119260, Singapore
SOURCE: Archives of Biochemistry and Biophysics (1999), 363(2), 267-272
CODEN: ABBIA4; ISSN: 0003-9861

PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB CD38 is a 46-kDa type II transmembrane glycoprotein that catalyzes the synthesis of cyclic ADP-ribose (**cADPR**) from NAD+. **CADPR** is a second messenger known to regulate intracellular Ca2+-induced Ca2+-release (CICR). A recent study has revealed that CD38 in Namalwa B cells undergoes internalization upon exposure to external NAD+. In this study, recombinant rat CD38 was expressed in Chinese hamster ovary (CHO) cells and the possibility that the protein undergoes internalization upon exposure to a substrate **analog** NADP+ was examined It was found that such treatment of CHO cells resulted in a decrease of ADP-ribosyl cyclase activity, as well as immunofluorescence of CD38 on the cell surface. The same treatment of CHO cells also resulted in intracellular clustering of CD38 mols. as revealed by confocal microscopic anal. The internalized CD38 was purified using a streptavidin/biotin-based method and was found to exhibit both ADP-ribosyl cyclase and **cADPR** hydrolase activities. On immunoblot, the internalized CD38 appeared as a monomer of 46 kDa under reducing **conditions** in SDS-PAGE. Our data demonstrate that NADP+ can efficiently induce internalization of CD38, a process that may be important in the production of **cADPR** intracellularly to regulate CICR. (c) 1999 Academic Press.
REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 7 OF 16 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:728317 CAPLUS
DOCUMENT NUMBER: 128:31474
TITLE: Mechanisms of calcium signaling by cyclic ADP-ribose and NAADP
AUTHOR(S): Cheung Lee, Hon
CORPORATE SOURCE: Department of Physiology, University of Minnesota, Minneapolis, MN, USA
SOURCE: Physiological Reviews (1997), 77(4), 1133-1164
CODEN: PHREA7; ISSN: 0031-9333
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with .apprx.188 refs. Cells possess various mechanisms for transducing external signals to intracellular responses. The discovery of inositol 1,4,5-trisphosphate (IP3) as a messenger for mobilizing internal Ca2+ stores has centralized Ca2+ mobilized among signaling mechanisms. Results reviewed in this article establish that, in addition to IP3, the internal Ca2+ stores can be mobilized by at least two other mols., cyclic ADP-ribose (**cADPR**) and nicotinic acid adenine dinucleotide phosphate (NAADP), via totally independent mechanisms. Cyclic ADP-ribose is a newly discovered cyclic nucleotide derived from NAD, but, unlike cAMP, its main signaling function of modulation of Ca2+-induced Ca2+ release, a major mechanism of Ca2+ mobilization in addition to the IP3 pathway. Evidence shows that **cADPR** may in fact be responsible for mediating the Ca2+-mobilizing activity of the gaseous messenger nitric oxide. Cells responsive to **cADPR** are widespread and include species from plant to mammal, indicating the generality of **cADPR** as a signaling mol. In addition to **cADPR**, NAADP, a metabolite of NADP, can also mobilize Ca2+ stores. The release mechanism and the stores on which NAADP acts are distinct from **cADPR** and IP3. Nicotinic acid adenine dinucleotide phosphate may play a role in generating Ca2+ oscillations, since liberation of NAADP in live cells by photolyzing its caged **analog** produces long-lasting Ca2+ oscillations. These two new Ca2+ agonists are intimately related, since the same metabolic enzymes can, under appropriate **conditions**, synthesize either one, suggesting a unified mechanism may regulate both pathways. Elucidation of these two new Ca2+ mobilization pathways is likely to have an important impact on our understanding of cellular signaling mechanisms.

REFERENCE COUNT: 188 THERE ARE 188 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 1 OF 18 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1061061 CAPLUS
DOCUMENT NUMBER: 143:419493
TITLE: Non-specific effects of 4-chloro-m-cresol may cause calcium flux and respiratory burst in human neutrophils
AUTHOR(S): Hauser, Carl J.; Kannan, Kolenkode B.; Deitch, Edwin A.; Itagaki, Kiyoshi
CORPORATE SOURCE: Department of Surgery, Division of Trauma, UMDNJ-New Jersey Medical School, Newark, NJ, 07103, USA
SOURCE: Biochemical and Biophysical Research Communications (2005), 336(4), 1087-1095
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We examined the effects of 4-chloro-m-cresol (4-CmC, a potent and specific activator of ryanodine receptors) on Ca2+-release/influx and respiratory burst in freshly isolated human PMN as well as HL60 cells. 4-CmC induces Ca2+ store-depletion in a dose-dependent manner at concns. between 400 μM and 3 mM, however no dose-dependent effect on Ca2+-influx was found. 4-CmC depleted Ca2+ stores that were shared with the GPC agonists such as fMLP and PAF, and therefore 4-CmC presumably depletes Ca2+ from ER. Since the authentic ligand for RyR is cyclic ADP-ribose (**cADPR**), we assessed the functional relevance of RyR in PMN by studying the presence and function of membrane-bound ADP-ribosyl cyclase (CD38) in PMN. First, expression of CD38 was confirmed by RT-PCR using cDNA from HL60 cells. Second, PMN from trauma **patients** showed significantly enhanced CD38 expression than those from healthy volunteers. In addition, although no chemotaxis effect was detected by 4-CmC, it stimulated respiratory burst in PMN in a dose-dependent manner. Our findings suggest that RyRs exist in human PMN and that RyR pathway may play an active role in inflammatory PMN calcium signaling. 8-Br-**cADPR** and cyclic 3-deaza-ADP did not have inhibitory effects either on 4-CmC-induced Ca2+ store-depletion or on respiratory burst, on the other hand, PLC inhibitor, U73122, completely attenuated both 4-CmC-induced Ca2+ store-depletion and respiratory burst. Although it has been used as a specific activator of RyR, 4-CmC has non-specific effects which cause Ca2+ store-depletion and respiratory burst at least in human PMN.
REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 2 OF 18 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:580098 CAPLUS
DOCUMENT NUMBER: 143:476129
TITLE: Altered Ca2+ Homeostasis in Human Uremic Skeletal Muscle: Possible Involvement of cADPR in Elevation of Intracellular Resting [Ca2+]
AUTHOR(S): Lopez, Jose R.; Mijares, Alfredo; Rojas, Bianca; Linares, Nancy; Allen, Paul D.; Shtifman, Alexander
CORPORATE SOURCE: Centro de Biofisica y Bioquimica, Instituto Venezolano de Investigaciones Cientificas (IVIC), Caracas, Venez.
SOURCE: Nephron (2005), 100(4), p51-p60
CODEN: NPRNAY; ISSN: 0028-2766
PUBLISHER: S. Karger AG
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Background: **Patients** with chronic renal failure may develop muscle weakness and fatigability due to disorders of skeletal muscle function, collectively known as the uremic myopathy. Cyclic ADP-ribose (**cADPR**), an endogenous metabolite of β-NAD+, activates Ca2+ release from intracellular stores in vertebrate and invertebrate cells. The current study investigated the possible role of **cADPR** in

uremic myopathy. Methods: We have examined the effect of **cADPR** on myoplasmic resting Ca2+ concentration ([Ca2+]i) in skeletal muscle obtained from control subjects and uremic **patients** (UP). [Ca2+]i was measured using double-barreled Ca2+-selective microelectrodes in muscle fibers, prior to and after microinjections of **cADPR**. Results: Resting [Ca2+]i was elevated in UP fibers compared with fibers obtained from control subjects. Removal of extracellular Ca2+, or incubation of cells with nifedipine, did not modify [Ca2+]i in UP or control fibers. Microinjection of **cADPR** produced an elevation of [Ca2+]i in both groups of cells. This elevation was not mediated by Ca2+ influx, or inhibited by heparin or ryanodine. [**cADPR**]i was determined to be higher in muscle fibers from UP compared to those from the control subjects. Incubation of cells with 8-bromo-**cADPR**, a **cADPR** antagonist, partially reduced [Ca2+]iin UP muscle fibers and blocked the **cADPR**-elicited elevation in [Ca2+]i in both groups of muscle cells. Conclusion: Skeletal muscles of the UP exhibit chronic elevation of [Ca2+]i that can be partially reduced by application of 8-bromo-**cADPR**. **cADPR** was able to mobilize Ca2+ from intracellular stores, by a mechanism that is independent of ryanodine or inositol trisphosphate receptors. It can be postulated that an alteration in the **cADPR**-signaling pathway may exist in skeletal muscle of the **patients** suffering from uremic myopathy.

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 3 OF 18 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:526112 CAPLUS

DOCUMENT NUMBER: 143:284609

TITLE: T-cell suppression mediated by mesenchymal stem cells is deficient in patients with severe aplastic anemia

AUTHOR(S): Bacigalupo, Andrea; Valle, Marisa; Podesta, Marina; Pitto, Anna; Zocchi, Elena; De Flora, Antonio; Pozzi, Sara; Luchetti, Silvia; Frassoni, Francesco; Van Lint, Maria Teresa; Piaggio, Giovanna

CORPORATE SOURCE: Divisione Ematologia Ospedale San Martino, Univ. degli Studi di Genova, Genoa, 16132, Italy

SOURCE: Experimental Hematology (New York, NY, United States) (2005), 33(7), 819-827
CODEN: EXHMA6; ISSN: 0301-472X

PUBLISHER: Elsevier Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Objective: To compare the suppressive effect of mesenchymal stem cells (MSC), derived from normal individuals or severe aplastic anemia **patients** (SAA), on T-cell activation. **Patients** and Methods: the authors studied bone marrow MSC from 19 healthy donors and 23 SAA **patients** in different phases of the disease: at diagnosis, following immunosuppressive therapy (IS), or after a bone marrow transplant (BMT). MSC were tested for T-cell suppression in the following assays: mixed lymphocyte reaction (MLR), phytohemagglutinin (PHA)-primed cultures, activation surface markers, γ-IFN production, hematopoietic colony formation (CFC), production of cyclic ADP-ribose (**cADPR**). Results: The abnormalities of SAA MSC included: 1) significantly lower suppression of T-cell proliferation induced by alloantigens or PHA; 2) impaired capacity to suppress CD38 expression on PHA-primed T cells; 3) impaired ability to suppress γ-IFN production in PHA cultures, resulting in an 11-fold higher γ-IFN concentration; 4) no preventive effect on T cell-mediated inhibition of CFC; and 5) significantly reduced production of **cADPR**, a universal calcium mobilizer. MSC-mediated suppression of PHA-induced T-cell proliferation was restored to control levels in 3 of 4 **patients** post-BMT. Conclusion: The ability of MSC to downregulate T-cell priming, proliferation, and cytokine release is deficient in **patients** with SAA, persists indefinitely after immunosuppressive

therapy, but seems to be restored after BMT. Whether these abnormalities are relevant to the pathogenesis of aplastic anemia remains to be determined

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 4 OF 18 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:259650 CAPLUS
DOCUMENT NUMBER: 142:291376
TITLE: Extracellular NAD+ and cyclic adenosine diphosphate ribose (cADPR) as potent antiinflammatory agents
INVENTOR(S): Fink, Mitchell P.; Delude, Russell L.; Han, Xianonan
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 18 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005065109	A1	20050324	US 2003-659063	20030910
PRIORITY APPLN. INFO.:			US 2003-659063	20030910

AB A method of prophylaxis or treatment of inflammatory conditions, including, but not limited to, intestinal epithelial inflammation due to intestine-specific conditions (e.g., Crohn's disease or ulcerative colitis) or systemic causes of inflammation (e.g., endotoxemia, sepsis, hemorrhagic shock/resuscitation or pancreatitis) is disclosed. In the method, an affected **patient** is administered a therapeutically effective amount of a composition including an NAD-related compound, in a form that is accessible to a receptor mol., conveyed in a pharmaceutically acceptable carrier vehicle. NAD-related compds. include NAD (NAD+), cyclic ADP ribose (**cADPR**), or functionally equivalent analogs, derivs., metabolites or agonists thereof, or prodrugs therefor. Also disclosed are ex vivo and in vivo assay methods to test candidate compds. for activity, kits for carrying out the therapeutic methods or the assay methods of the invention and articles of manufacture that include compns. for use in the methods of the invention and instructions for the use thereof.

L19 ANSWER 5 OF 18 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:991982 CAPLUS
DOCUMENT NUMBER: 142:91628
TITLE: CD38 autoimmunity: recent advances and relevance to human diabetes
AUTHOR(S): Antonelli, A.; Ferrannini, E.
CORPORATE SOURCE: Metabolism Unit, Department of Internal Medicine and CNR Institute of Clinical Physiology, University of Pisa School of Medicine, Pisa, Italy
SOURCE: Journal of Endocrinological Investigation (2004), 27(7), 695-707
CODEN: JEIND7; ISSN: 0391-4097
PUBLISHER: Editrice Kurtis s.r.l.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Human CD38 is a protein which catalyzes the synthesis of nicotinic acid adenine dinucleotide (NAADP+) and the conversion of NAD+ to **cADPR**. Both **cADPR** and NAADP+ are powerful intracellular Ca2+ ([Ca2+]i) mobilizers in different cell types. Recently, the presence of CD38 autoantibodies has been found in a significant number (9-15%) of **patients** with Type 2 or long-standing Type 1 diabetes. These autoantibodies are biol. active, the majority of them (.apprx.60%) displaying agonistic properties, i.e., [Ca2+]i mobilization in lymphocytic cell lines and in pancreatic islets. In cultured rat pancreatic islets,

the human autoantibodies inhibit glucose-induced insulin release, whereas, in human pancreatic islets CD38 autoantibodies stimulate glucose-mediated insulin secretion. The clin. phenotype of anti-CD38-pos. Type 2 diabetes differs from the LADA (latent autoimmune diabetes of adults) phenotype. When accurately matched for age and obesity, only LADA **patients** with anti-GAD antibodies, but not GAD-neg./CD38-pos. **patients**, have reduced in vivo β-cell function in comparison to antibody-neg. **patients**. Transgenic mice overexpressing CD38 show enhanced glucose-induced insulin release, whereas, conversely, CD38 knockout mice display a severe impairment in β-cell function. Few Japanese diabetic **patients** carry a missense mutation in the CD38 gene; in Caucasian **patients** mutations in the CD38 gene have not been found. Collectively, these findings suggest that activation of CD38 represents an alternative signaling pathway for glucose-induced insulin secretion in human β-cells. More information, however, is necessary to gauge the role of CD38 autoimmunity in the context of the natural history of human Type 1 or Type 2 diabetes.

REFERENCE COUNT: 90 THERE ARE 90 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 6 OF 18 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2000:716727 CAPLUS
DOCUMENT NUMBER: 134:309306
TITLE: Physiological and pathological significance of the CD38-cyclic ADP-ribose signaling system
AUTHOR(S): Okamoto, Hiroshi; Takasawa, Shin; Nata, Koji; Kato, Ichiro; Tohgo, Akira; Noguchi, Naoya
CORPORATE SOURCE: Department of Biochemistry, Tohoku University Graduate School of Medicine, Sendai, Japan
SOURCE: Chemical Immunology (2000), 75(Human CD38 and Related Molecules), 121-145
CODEN: CHMIEP; ISSN: 1015-0145
PUBLISHER: S. Karger AG
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 87 refs. Topics discussed include the importance of the maintenance of cellular NAD+ levels for β-cell functioning; cyclic ADP-ribose (**cADPR**) accumulation in islets in response to glucose stimulation; the mechanism of **cADPR** accumulation in islets; cysteine residues essential for **cADPR** hydrolase of CD38; Ca2+ release by **cADPR** from islet microsomes and insulin secretion from permeabilized islets; the activation of Ca2+ release by Ca2+/calmodulin-dependent protein kinase II; insulin secretion in CD38-transgenic and CD38 gene-disrupted mice; the structures of human CD38 gene and its related genes; and CD38 gene mutation found in noninsulin-dependent diabetes **patients**.

REFERENCE COUNT: 87 THERE ARE 87 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 7 OF 18 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1998:569192 CAPLUS
DOCUMENT NUMBER: 129:147626
TITLE: A missense mutation in the CD38 gene, a novel factor for insulin secretion. Association with type II diabetes mellitus in Japanese subjects and evidence of abnormal function when expressed in vitro
AUTHOR(S): Yagui, K.; Shimada, F.; Mimura, M.; Hashimoto, N.; Suzuki, Y.; Tokuyama, Y.; Nata, K.; Tohgo, A.; Ikehata, F.; Takasawa, S.; Okamoto, H.; Makino, H.; Saito, Y.; Kanatsuka, Azuma
CORPORATE SOURCE: Department Internal Medicine II, School Medicine, Chiba University, Chiba, 260, Japan
SOURCE: Diabetologia (1998), 41(9), 1024-1028
CODEN: DBTGAJ; ISSN: 0012-186X

PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Cyclic adenosine 5'diphosphate-ribose (**cADPR**) is thought to have a second messenger role in insulin secretion through mobilization of Ca2+. As human lymphocyte antigen CD38 has both ADP-ribosyl cyclase and **cADPR** hydrolase activity, it may be important in glucose-induced insulin secretion in islets. Thirty one randomly selected Japanese **patients** with Type II diabetes mellitus who had first-degree and/or second-degree relative(s) with Type II diabetes mellitus were screened for mutations of this gene using single-stranded conformation polymorphism. Two variant patterns in exon 3 and exon 4 of the CD38 gene were identified. The variant in exon 3 resulted in an amino acid substitution from Arg140 (CGG) to Trp (TGG). The Arg140Trp mutation was observed in 4 of 31 **patients**, and allele frequencies were significantly different in **patients** and the control subjects ($p = 0.004$). One **patient** with this mutation has two missense mutations on beta cell/liver glucose transporter (GLUT2) gene; her mother, who has impaired glucose tolerance, also has this mutation on the CD38 gene and one missense mutation on the GLUT2 gene. Enzyme activity studies using COS-7 cells expressing the Arg140Trp mutation showed a reduction in ADP-ribosyl cyclase and **cADPR** hydrolase activity of around 50%. The Arg140Trp mutation on CD38 thus appears to contribute to the development of Type II diabetes mellitus via the impairment of glucose-induced insulin secretion in the presence of other genetic defects.

L19 ANSWER 8 OF 18 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:477762 CAPLUS
DOCUMENT NUMBER: 129:202031
TITLE: Autoantibodies against CD38 (ADP-ribosyl cyclase/cyclic ADP-ribose hydrolase) that impair glucose-induced insulin secretion in noninsulin-dependent diabetes patients
AUTHOR(S): Ikehata, Fumiko; Satoh, Jo; Nata, Koji; Tohgo, Akira; Nakazawa, Tetsuya; Kato, Ichiro; Kobayashi, Seiichi; Akiyama, Takako; Takasawa, Shin; Toyota, Takayoshi; Okamoto, Hiroshi
CORPORATE SOURCE: Department of Biochemistry, Tohoku University School of Medicine, Sendai, 980-8575, Japan
SOURCE: Journal of Clinical Investigation (1998), 102(2), 395-401
CODEN: JCINAO; ISSN: 0021-9738
PUBLISHER: Rockefeller University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Cyclic ADP-ribose (**cADPR**) has been shown to be a mediator for intracellular Ca2+ mobilization for insulin secretion by glucose in pancreatic β cells, and CD38 shows both ADP-ribosyl cyclase to synthesize **cADPR** from NAD+ and **cADPR** hydrolase activity to hydrolyze **cADPR** to ADP-ribose. The authors show here that 13.8% of Japanese non-insulin-dependent diabetes (NIDDM) **patients** examined have autoantibodies against CD38 and that the sera containing anti-CD38 autoantibodies inhibit the ADP-ribosyl cyclase activity of CD38. Insulin secretion from pancreatic islets by glucose is inhibited by the addition of the NIDDM sera with anti-CD38 antibodies, and the inhibition of insulin secretion is abolished by the addition of recombinant CD38. The increase of **cADPR** levels in pancreatic islets by glucose was also inhibited by the addition of the sera. Thus, the presence of anti-CD38 autoantibodies in NIDDM **patients** can be one of the major causes of impaired glucose-induced insulin secretion in NIDDM.
REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 9 OF 18 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:711016 CAPLUS
DOCUMENT NUMBER: 126:6043
TITLE: Identification and characterization of an active soluble form of human CD38 in normal and pathological fluids
AUTHOR(S): Funaro, Ada; Horenstein, Alberto L.; Calosso, Liliana; Morra, Massimo; Tarocco, Renzo P.; Franco, Luisa; De Flora, Antonio; Malavasi, Fabio
CORPORATE SOURCE: Dep. Genetics, Univ. Turin, Turin, Italy
SOURCE: International Immunology (1996), 8(11), 1643-1650
CODEN: INIMEN; ISSN: 0953-8178
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Human CD38 is a transmembrane glycoprotein involved in lymphocyte activation and adhesion to endothelium. The ectocellular domain of the mol. possesses properties of a bifunctional enzyme catalyzing both the synthesis from NAD+ and the hydrolysis of the calcium-releasing metabolite cyclic ADP-ribose (**cADPR**). Surface expression of CD38 (mCD38) is rapidly and almost completely down-modulated upon ligation by specific mAb in cells from different lineages. The data presented here also show that, in addition to the existence of a mCD38, a soluble form of CD38 (sCD38) is detectable in the cell culture supernatant of allo-activated T lymphocytes and of several tumor cell lines. SCD38 is also present in vivo and is assayable in normal (fetal serum and amniotic fluid) and pathol. (serum and ascites from **patients** with multiple myeloma, and serum from **patients** with AIDS) biol. fluids. Immunoaffinity chromatog., SDS-PAGE and Western blot analyses with mAb and polyclonal antibodies, along with metabolic labeling, yield a body of data concerning the structure of sCD38, which displays a Mr of 39 kDa. Native sCD38 maintains the ability to inhibit the binding activity of different anti-CD38 mAb and still catalyzes the synthesis and the hydrolysis of **cADPR** at the same ratio observed with mCD38. Furthermore, crosslinking expts. indicate that the purified soluble mol. binds a 120 kDa mol. expressed by monocytoid cells and identified as a candidate ligand for human mCD38.

L19 ANSWER 10 OF 18 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:681589 CAPLUS
DOCUMENT NUMBER: 125:325707
TITLE: Selective induction of CD73 expression in human lymphocytes by CD38 ligation. A novel pathway linking signal transducers with ecto-enzyme activities
AUTHOR(S): Peola, Silvia; Borrione, Paolo; Matera, Lina; Malavasi, Fabio; Pileri, Alessandro; Massaia, Massimo
CORPORATE SOURCE: Hiv. Hematol., Univ. Torino, Turin, 10126, Italy
SOURCE: Journal of Immunology (1996), 157(10), 4354-4362
CODEN: JOIMA3; ISSN: 0022-1767
PUBLISHER: American Association of Immunologists
DOCUMENT TYPE: Journal
LANGUAGE: English
AB CD73 is a glycosyl phosphatidylinositol (GPI)-anchored purine salvage enzyme (ecto-5'-nucleotidase (ecto-5'-NT), E.C. 3.1.3.5) whose expression on lymphocytes is dependent on their differentiation state and function. CD73 behaves as an agonistic mol. in signaling via the CD3/TCR and CD2 pathways and is associated with CTL generation, IgG production, and activation of resting naive CD8+ T cells. CD73 deficiency has been reported in a variety of **patients** with impaired T and/or B cell function. Thus, CD73 holds promise as a mol. target for intervention in the immune system, but the mechanisms regulating its expression are largely unknown. The aim of this study was to gain insight into the regulation of CD73 expression in human lymphocytes. CD38, another cell surface

differentiation Ag with ecto-enzyme activities (NAD+ glycohydrolase, ADP-ribosyl cyclase, and cyclic ADP-ribose (**cADPR**) hydrolase), was found to specifically induce CD73 expression in T and B cell lines as well as in normal adult T and NK cells, cord blood T cells, and thymocytes. CD38 crosslinking induced a rapid export to the cell surface of pre-formed CD73 derived from an intracellular pool and not from de novo biosynthesis. This translocation was dependent on protein tyrosine kinase (PTK) activity and lasted approx. eight hours, after which CD73 was removed from the cell surface by enzymic cleavage. CD73 was not induced by other agents that activate T cells and CD73 was the only GPI-anchored mol. up-regulated by CD38 ligation out of six analyzed. These results document a novel pathway in human lymphocytes leading from CD38 ligation to CD73 expression, which may result in the rapid acquisition of new functions, including increased purine salvage, increased sensitivity to Ag-induced activation, and the generation of adenosine (Ado) for Ado receptor signaling.

L19 ANSWER 11 OF 18 MEDLINE on STN
ACCESSION NUMBER: 2005523230 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16168959
TITLE: Non-specific effects of 4-chloro-m-cresol may cause calcium flux and respiratory burst in human neutrophils.
AUTHOR: Hauser Carl J; Kannan Kolenkode B; Deitch Edwin A; Itagaki Kiyoshi
CORPORATE SOURCE: The Department of Surgery, Division of Trauma, UMDNJ-New Jersey Medical School, Newark, 07103, USA.
SOURCE: Biochemical and biophysical research communications, (2005 Nov 4) Vol. 336, No. 4, pp. 1087-95.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200512
ENTRY DATE: Entered STN: 4 Oct 2005
Last Updated on STN: 18 Dec 2005
Entered Medline: 12 Dec 2005

AB We examined the effects of 4-chloro-m-cresol (4-CmC, a potent and specific activator of ryanodine receptors) on Ca(2+)-release/influx and respiratory burst in freshly isolated human PMN as well as HL60 cells. 4-CmC induces Ca(2+) store-depletion in a dose-dependent manner at concentrations between 400muM and 3mM, however no dose-dependent effect on Ca(2+)-influx was found. 4-CmC depleted Ca(2+) stores that were shared with the GPC agonists such as fMLP and PAF, and therefore 4-CmC presumably depletes Ca(2+) from ER. Since the authentic ligand for RyR is cyclic ADP-ribose (**cADPR**), we assessed the functional relevance of RyR in PMN by studying the presence and function of membrane-bound ADP-ribosyl cyclase (CD38) in PMN. First, expression of CD38 was confirmed by RT-PCR using cDNA from HL60 cells. Second, PMN from trauma **patients** showed significantly enhanced CD38 expression than those from healthy volunteers. In addition, although no chemotaxis effect was detected by 4-CmC, it stimulated respiratory burst in PMN in a dose-dependent manner. Our findings suggest that RyRs exist in human PMN and that RyR pathway may play an active role in inflammatory PMN calcium signaling. 8-Br-**cADPR** and cyclic 3-deaza-ADP did not have inhibitory effects either on 4-CmC-induced Ca(2+) store-depletion or on respiratory burst, on the other hand, PLC inhibitor, U73122, completely attenuated both 4-CmC-induced Ca(2+) store-depletion and respiratory burst. Although it has been used as a specific activator of RyR, 4-CmC has non-specific effects which cause Ca(2+) store-depletion and respiratory burst at least in human PMN.

L19 ANSWER 12 OF 18 MEDLINE on STN
ACCESSION NUMBER: 2005339665 MEDLINE

DOCUMENT NUMBER: PubMed ID: 15855809
TITLE: Altered Ca2+ homeostasis in human uremic skeletal muscle: possible involvement of cADPR in elevation of intracellular resting [Ca2+].
AUTHOR: Lopez Jose R; Mijares Alfredo; Rojas Bianca; Linares Nancy; Allen Paul D; Shtifman Alexander
CORPORATE SOURCE: Centro de Biofisica y Bioquimica, Instituto Venezolano de Investigaciones Cientificas, Caracas, Venezuela.. lopez@zeus.bwh.harvard.edu
CONTRACT NUMBER: R01AR46513 (NIAMS)
SOURCE: Nephron. Physiology [electronic resource], (2005) Vol. 100, No. 4, pp. p51-60. Electronic Publication: 2005-04-25. Journal code: 101159772. E-ISSN: 1660-2137.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200603
ENTRY DATE: Entered STN: 2 Jul 2005
Last Updated on STN: 15 Mar 2006
Entered Medline: 14 Mar 2006

AB BACKGROUND: **Patients** with chronic renal failure may develop muscle weakness and fatigability due to disorders of skeletal muscle function, collectively known as the uremic myopathy. Cyclic adenosine diphosphate-ribose (**cADPR**), an endogenous metabolite of beta-NAD+, activates Ca2+ release from intracellular stores in vertebrate and invertebrate cells. The current study investigated the possible role of **cADPR** in uremic myopathy. METHODS: We have examined the effect of **cADPR** on myoplasmic resting Ca2+ concentration ([Ca2+]i) in skeletal muscle obtained from control subjects and uremic **patients** (UP). [Ca2+]i was measured using double-barreled Ca2+-selective microelectrodes in muscle fibers, prior to and after microinjections of **cADPR**. RESULTS: Resting [Ca2+]i was elevated in UP fibers compared with fibers obtained from control subjects. Removal of extracellular Ca2+, or incubation of cells with nifedipine, did not modify [Ca2+]i in UP or control fibers. Microinjection of **cADPR** produced an elevation of [Ca2+]i in both groups of cells. This elevation was not mediated by Ca2+ influx, or inhibited by heparin or ryanodine. [**cADPR**]i was determined to be higher in muscle fibers from UP compared to those from the control subjects. Incubation of cells with 8-bromo-**cADPR**, a **cADPR** antagonist, partially reduced [Ca2+]i in UP muscle fibers and blocked the **cADPR**-elicited elevation in [Ca2+]i in both groups of muscle cells. CONCLUSION: Skeletal muscles of the UP exhibit chronic elevation of [Ca2+]i that can be partially reduced by application of 8-bromo-**cADPR**. **cADPR** was able to mobilize Ca2+ from intracellular stores, by a mechanism that is independent of ryanodine or inositol trisphosphate receptors. It can be postulated that an alteration in the **cADPR**-signaling pathway may exist in skeletal muscle of the **patients** suffering from uremic myopathy.

L19 ANSWER 13 OF 18 MEDLINE on STN
ACCESSION NUMBER: 2005315700 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15963858
TITLE: T-cell suppression mediated by mesenchymal stem cells is deficient in patients with severe aplastic anemia.
AUTHOR: Bacigalupo Andrea; Valle Marisa; Podesta Marina; Pitto Anna; Zocchi Elena; De Flora Antonio; Pozzi Sara; Luchetti Silvia; Frassoni Francesco; Van Lint Maria Teresa; Piaggio Giovanna
CORPORATE SOURCE: Divisione Ematologia Ospedale San Martino, Italy.
SOURCE: Experimental hematology, (2005 Jul) Vol. 33, No. 7, pp. 819-27.
Journal code: 0402313. ISSN: 0301-472X.

PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200509
ENTRY DATE: Entered STN: 21 Jun 2005
Last Updated on STN: 20 Sep 2005
Entered Medline: 19 Sep 2005

AB OBJECTIVE: To compare the suppressive effect of mesenchymal stem cells (MSC), derived from normal individuals or severe aplastic anemia **patients** (SAA), on T-cell activation. **PATIENTS** AND METHODS: We studied bone marrow MSC from 19 healthy donors and 23 SAA **patients** in different phases of the disease: at diagnosis (n = 3), following immunosuppressive therapy (IS) (n = 16), or after a bone marrow transplant (BMT) (n = 4). MSC were tested for T-cell suppression in the following assays: mixed lymphocyte reaction (MLR), phytohemaglutinin (PHA)-primed cultures, activation surface markers, gamma-IFN production, hematopoietic colony formation (CFC), production of cyclic ADP-ribose (**cADPR**). RESULTS: The abnormalities of SAA MSC included: 1) significantly lower suppression of T-cell proliferation induced by alloantigens (p = 0.009) or PHA (p = 0.006); 2) impaired capacity to suppress CD38 expression on PHA-primed T cells (p = 0.001); 3) impaired ability to suppress gamma-IFN production in PHA cultures, resulting in an 11-fold higher gamma-IFN concentration; 4) no preventive effect on T cell-mediated inhibition of CFC; and 5) significantly reduced (p = 0.009) production of **cADPR**, a universal calcium mobilizer. MSC-mediated suppression of PHA-induced T-cell proliferation was restored to control levels in 3 of 4 **patients** post-BMT. CONCLUSION: The ability of MSC to downregulate T-cell priming, proliferation, and cytokine release is deficient in **patients** with SAA, persists indefinitely after immunosuppressive therapy, but seems to be restored after BMT. Whether these abnormalities are relevant to the pathogenesis of aplastic anemia remains to be determined.

L19 ANSWER 14 OF 18 MEDLINE on STN
ACCESSION NUMBER: 2004535071 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15505998
TITLE: CD38 autoimmunity: recent advances and relevance to human diabetes.
AUTHOR: Antonelli A; Ferrannini E
CORPORATE SOURCE: Metabolism Unit, Department of Internal Medicine and CNR Institute of Clinical Physiology, University of Pisa School of Medicine, Pisa, Italy.. a.antonelli@med.unipi.it
SOURCE: Journal of endocrinological investigation, (2004 Jul-Aug) Vol. 27, No. 7, pp. 695-707. Ref: 90
Journal code: 7806594. ISSN: 0391-4097.
PUB. COUNTRY: Italy
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200502
ENTRY DATE: Entered STN: 28 Oct 2004
Last Updated on STN: 16 Feb 2005
Entered Medline: 15 Feb 2005

AB Human CD38 is a protein which catalyzes the synthesis of nicotinic acid adenine dinucleotide (NAADP+) and the conversion of NAD+ to **cADPR** . Both **cADPR** and NAADP+ are powerful intracellular Ca2+ ([Ca2+]i) mobilizers in different cell types. Recently, the presence of CD38 autoantibodies has been found in a significant number (9-15%) of **patients** with Type 2 or long-standing Type 1 diabetes. These autoantibodies are biologically active, the majority of them (-60%) displaying agonistic properties, i.e., [Ca2+]i mobilization in lymphocytic cell lines and in pancreatic islets. In cultured rat pancreatic islets,

the human autoantibodies inhibit glucose-induced insulin release, whereas, in human pancreatic islets CD38 autoantibodies stimulate glucose-mediated insulin secretion. The clinical phenotype of anti-CD38-positive Type 2 diabetes differs from the LADA (latent autoimmune diabetes of adults) phenotype. When accurately matched for age and obesity, only LADA **patients** with anti-GAD antibodies, but not GAD-negative/ CD38-positive **patients**, have reduced in vivo beta-cell function in comparison to antibody-negative **patients**. Transgenic mice overexpressing CD38 show enhanced glucose-induced insulin release, whereas, conversely, CD38 knockout mice display a severe impairment in beta-cell function. Few Japanese diabetic **patients** carry a missense mutation in the CD38 gene; in Caucasian **patients** mutations in the CD38 gene have not been found. Collectively, these findings suggest that activation of CD38 represents an alternative signaling pathway for glucose-induced insulin secretion in human beta-cells. More information, however, is necessary to gauge the role of CD38 autoimmunity in the context of the natural history of human Type 1 or Type 2 diabetes.

L19 ANSWER 15 OF 18 MEDLINE on STN
ACCESSION NUMBER: 1998425815 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9754820
TITLE: A missense mutation in the CD38 gene, a novel factor for insulin secretion: association with Type II diabetes mellitus in Japanese subjects and evidence of abnormal function when expressed in vitro.
AUTHOR: Yagui K; Shimada F; Mimura M; Hashimoto N; Suzuki Y; Tokuyama Y; Nata K; Tohgo A; Ikehata F; Takasawa S; Okamoto H; Makino H; Saito Y; Kanatsuka A
CORPORATE SOURCE: Department of Internal Medicine II, Chiba University School of Medicine, Japan.
SOURCE: Diabetologia, (1998 Sep) Vol. 41, No. 9, pp. 1024-8. Journal code: 0006777. ISSN: 0012-186X.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 15 Jan 1999
Last Updated on STN: 18 Dec 2002
Entered Medline: 10 Dec 1998

AB Cyclic adenosine 5'diphosphate-ribose (**cADPR**) is thought to have a second messenger role in insulin secretion through mobilisation of Ca2+. As human lymphocyte antigen CD38 has both ADP-ribosyl cyclase and **cADPR** hydrolase activity, it may be important in glucose-induced insulin secretion in islets. Thirty one randomly selected Japanese **patients** with Type II diabetes mellitus who had first-degree and/or second-degree relative(s) with Type II diabetes mellitus were screened for mutations of this gene using single-stranded conformation polymorphism. Two variant patterns in exon 3 and exon 4 of the CD38 gene were identified. The variant in exon 3 resulted in an amino acid substitution from Arg140 (CGG) to Trp (TGG). The Arg140Trp mutation was observed in 4 of 31 **patients**, and allele frequencies were significantly different in **patients** and the control subjects ($p = 0.004$). One **patient** with this mutation has two missense mutations on beta cell/liver glucose transporter (GLUT2) gene; her mother, who has impaired glucose tolerance, also has this mutation on the CD38 gene and one missense mutation on the GLUT2 gene. Enzyme activity studies using COS-7 cells expressing the Arg140Trp mutation showed a reduction in ADP-ribosyl cyclase and **cADPR** hydrolase activity of around 50%. The Arg140Trp mutation on CD38 thus appears to contribute to the development of Type II diabetes mellitus via the impairment of glucose-induced insulin secretion in the presence of other genetic defects.

L19 ANSWER 16 OF 18 MEDLINE on STN
ACCESSION NUMBER: 1998330466 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9664081
TITLE: Autoantibodies against CD38 (ADP-ribosyl cyclase/cyclic ADP-ribose hydrolase) that impair glucose-induced insulin secretion in noninsulin- dependent diabetes patients.
AUTHOR: Ikehata F; Satoh J; Nata K; Tohgo A; Nakazawa T; Kato I; Kobayashi S; Akiyama T; Takasawa S; Toyota T; Okamoto H
CORPORATE SOURCE: Department of Biochemistry, Tohoku University School of Medicine, Sendai 980-8575, Japan.
SOURCE: The Journal of clinical investigation, (1998 Jul 15) Vol. 102, No. 2, pp. 395-401.
Journal code: 7802877. ISSN: 0021-9738.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199808
ENTRY DATE: Entered STN: 28 Aug 1998
Last Updated on STN: 18 Dec 2002
Entered Medline: 20 Aug 1998

AB Cyclic ADP-ribose (**cADPR**) has been shown to be a mediator for intracellular Ca2+ mobilization for insulin secretion by glucose in pancreatic beta cells, and CD38 shows both ADP-ribosyl cyclase to synthesize **cADPR** from NAD+ and **cADPR** hydrolase to hydrolyze **cADPR** to ADP-ribose. We show here that 13.8% of Japanese non-insulin-dependent diabetes (NIDDM) **patients** examined have autoantibodies against CD38 and that the sera containing anti-CD38 autoantibodies inhibit the ADP-ribosyl cyclase activity of CD38 (P </= 0.05). Insulin secretion from pancreatic islets by glucose is significantly inhibited by the addition of the NIDDM sera with anti-CD38 antibodies (P </= 0.04-0.0001), and the inhibition of insulin secretion is abolished by the addition of recombinant CD38 (P </= 0.02). The increase of **cADPR** levels in pancreatic islets by glucose was also inhibited by the addition of the sera (P </= 0.05). These results strongly suggest that the presence of anti-CD38 autoantibodies in NIDDM **patients** can be one of the major causes of impaired glucose-induced insulin secretion in NIDDM.

L19 ANSWER 17 OF 18 MEDLINE on STN
ACCESSION NUMBER: 97098943 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8943558
TITLE: Identification and characterization of an active soluble form of human CD38 in normal and pathological fluids.
AUTHOR: Funaro A; Horenstein A L; Calosso L; Morra M; Tarocco R P; Franco L; De Flora A; Malavasi F
CORPORATE SOURCE: Department of Genetics, Biology and Medical Chemistry, University of Turin, Italy.
SOURCE: International immunology, (1996 Nov) Vol. 8, No. 11, pp. 1643-50.
Journal code: 8916182. ISSN: 0953-8178.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199703
ENTRY DATE: Entered STN: 13 Mar 1997
Last Updated on STN: 18 Dec 2002
Entered Medline: 3 Mar 1997

AB Human CD38 is a transmembrane glycoprotein involved in lymphocyte activation and adhesion to endothelium. The ectocellular domain of the molecule possesses properties of a bifunctional enzyme catalyzing both the synthesis from NAD+ and the hydrolysis of the calcium-releasing metabolite

cyclic ADP-ribose (**cADPR**). Surface expression of CD38 (mCD38) is rapidly and almost completely down-modulated upon ligation by specific mAb in cells from different lineages. The data presented here also show that, in addition to the existence of a mCD38, a soluble form of CD38 (sCD38) is detectable in the cell culture supernatant of allo-activated T lymphocytes and of several tumor cell lines. sCD38 is also present in vivo and is assayable in normal (fetal serum and amniotic fluid) and pathological (serum and ascites from **patients** with multiple myeloma, and serum from **patients** with AIDS) biological fluids. Immunoaffinity chromatography, SDS-PAGE and Western blot analyses with mAb and polyclonal antibodies, along with metabolic labeling, yield a body of data concerning the structure of sCD38, which displays a M(r) of 39 kDa. Native sCD38 maintains the ability to inhibit the binding activity of different anti-CD38 mAb and still catalyzes the synthesis and the hydrolysis of **cADPR** at the same ratio observed with mCD38. Furthermore, cross-linking experiments indicate that the purified soluble molecule binds a 120 kDa molecule expressed by monocytoid cells and identified as a candidate ligand for human mCD38.

L19 ANSWER 18 OF 18 MEDLINE on STN
ACCESSION NUMBER: 97064191 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8906810
TITLE: Selective induction of CD73 expression in human lymphocytes by CD38 ligation: a novel pathway linking signal transducers with ecto-enzyme activities.
AUTHOR: Peola S; Borrione P; Matera L; Malavasi F; Pileri A; Massaia M
CORPORATE SOURCE: Division of Hematology of the University of Torino, Italy.
SOURCE: Journal of immunology (Baltimore, Md. : 1950), (1996 Nov 15) Vol. 157, No. 10, pp. 4354-62.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 28 Jan 1997
Last Updated on STN: 18 Dec 2002
Entered Medline: 31 Dec 1996

AB CD73 is a glycosyl phosphatidylinositol (GPI)-anchored purine salvage enzyme (ecto-5'-nucleotidase (ecto-5'-NT), E.C. 3.1.3.5) whose expression on lymphocytes is dependent on their differentiation state and function. CD73 behaves as an agonistic molecule in signaling via the CD3/TCR and CD2 pathways and is associated with CTL generation, IgG production, and activation of resting naive CD8+ T cells. CD73 deficiency has been reported in a variety of **patients** with impaired T and/or B cell function. Thus, CD73 holds promise as a molecular target for intervention in the immune system, but the mechanisms regulating its expression are largely unknown. The aim of this study was to gain insight into the regulation of CD73 expression in human lymphocytes. CD38, another cell surface differentiation Ag with ecto-enzyme activities (NAD+ glycohydrolase, ADP-ribosyl cyclase, and cyclic ADP-ribose (**cADPR**) hydrolase), was found to specifically induce CD73 expression in T and B cell lines as well as in normal adult T and NK cells, cord blood T cells, and thymocytes. CD38 cross-linking induced a rapid export to the cell surface of pre-formed CD73 derived from an intracellular pool and not from de novo biosynthesis. This translocation was dependent on protein tyrosine kinase (PTK) activity and lasted approximately eight hours, after which CD73 was removed from the cell surface by enzymatic cleavage. CD73 was not induced by other agents that activate T cells and CD73 was the only GPI-anchored molecule up-regulated by CD38 ligation out of six analyzed. These results document a novel pathway in human lymphocytes leading from CD38 ligation to CD73 expression, which may result in the rapid acquisition of new functions, including increased purine salvage,

increased sensitivity to Ag-induced activation, and the generation of adenosine (Ado) for Ado receptor signaling.

L20 ANSWER 4 OF 4 MEDLINE on STN
ACCESSION NUMBER: 97223785 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9070427
TITLE: 7-Deaza cyclic adenosine 5'-diphosphate ribose: first example of a Ca(2+)-mobilizing partial agonist related to cyclic adenosine 5'-diphosphate ribose.
AUTHOR: Bailey V C; Sethi J K; Fortt S M; Galione A; Potter B V
CORPORATE SOURCE: Department of Medicinal Chemistry, School of Pharmacy and Pharmacology, University of Bath, UK.
SOURCE: Chemistry & biology, (1997 Jan) Vol. 4, No. 1, pp. 51-61. Journal code: 9500160. ISSN: 1074-5521.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199706
ENTRY DATE: Entered STN: 30 Jun 1997
Last Updated on STN: 3 Mar 2000
Entered Medline: 16 Jun 1997

AB BACKGROUND: Cyclic adenosine 5'-diphosphate ribose (**cADPR**), a naturally occurring metabolite of nicotinamide adenine dinucleotide (NAD+), mobilizes Ca2+ from non-mitochondrial stores in a variety of mammalian and invertebrate tissues. It has been shown that **cADPR** activates ryanodine-sensitive Ca(2+)-release channels, working independently of inositol 1,4,5-trisphosphate (IP3) to mobilize intracellular Ca2+ stores. In some systems, **cADPR** has been shown to be more potent than IP3. The chemo-enzymatic synthesis of structurally modified analogues of **cADPR** can provide pharmacological tools for probing this new Ca(2+)-signaling pathway. In this work, we describe the synthesis and evaluation of a structural mimic of **cADPR** with different Ca(2+)-releasing properties. RESULTS: 7-Deaza cyclic adenosine 5'-diphosphate ribose (7-deaza **cADPR**), a novel **cADPR** analogue modified in the purine ring, was synthesized and its ability to release Ca2+ from non-mitochondrial pools in homogenates made from sea urchin eggs was investigated. 7-Deaza **cADPR** was more effective in releasing Ca2+ than **cADPR**, but it only released approximately 66% of the Ca2+ released by a maximal concentration of **cADPR**. It was also more resistant to hydrolysis than **cADPR**. If we **administered** increasing concentrations of 7-deaza **cADPR** at the same time as a maximal concentration of **cADPR**, the induction of Ca2+ release by **cADPR** was antagonized. CONCLUSIONS: 7-Deaza **cADPR** has a Ca(2+)-release profile consistent with that of a partial agonist, and it is the first reported example of such a compound to act at the **cADPR** receptor. The imidazole ring of **cADPR** is clearly important in stimulating the Ca(2+)-release machinery, and the present results demonstrate that structural modification of a site other than position 8 of the purine ring can affect the efficacy of Ca2+ release. 7-Deaza **cADPR** represents a significant step forwards in designing modulators of the **cADPR** signaling pathway.

L20 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:259650 CAPLUS
DOCUMENT NUMBER: 142:291376
TITLE: Extracellular NAD+ and cyclic adenosine diphosphate ribose (cADPR) as potent antiinflammatory agents
INVENTOR(S): Fink, Mitchell P.; Delude, Russell L.; Han, Xianonan
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 18 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005065109	A1	20050324	US 2003-659063	20030910

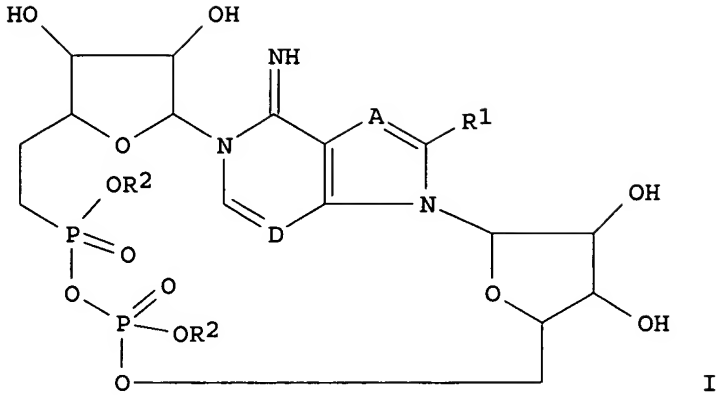
PRIORITY APPLN. INFO.: US 2003-659063 20030910

AB A method of prophylaxis or treatment of inflammatory conditions, including, but not limited to, intestinal epithelial inflammation due to intestine-specific conditions (e.g., Crohn's disease or ulcerative colitis) or systemic causes of inflammation (e.g., endotoxemia, sepsis, hemorrhagic shock/resuscitation or pancreatitis) is disclosed. In the method, an affected patient is **administered** a therapeutically effective amount of a composition including an NAD-related compound, in a form that is accessible to a receptor mol., conveyed in a pharmaceutically acceptable carrier vehicle. NAD-related compds. include NAD (NAD+), cyclic ADP ribose (**cADPR**), or functionally equivalent analogs, derivs., metabolites or agonists thereof, or prodrugs therefor. Also disclosed are ex vivo and in vivo assay methods to test candidate compds. for activity, kits for carrying out the therapeutic methods or the assay methods of the invention and articles of manufacture that include compns. for use in the methods of the invention and instructions for the use thereof.

L20 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:545762 CAPLUS
DOCUMENT NUMBER: 139:95491
TITLE: Cyclic-ADP-ribose analogs
INVENTOR(S): Walseth, Timothy F.; De Flora, Antonio; Zocchi, Elena; Podesta, Marina; Wong, Long; Aarhus, Robert A.; Lee, Hon Cheung
PATENT ASSIGNEE(S): Regents of the University of Minnesota, USA
SOURCE: U.S., 22 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6593307	B1	20030715	US 2000-698611	20001027

PRIORITY APPLN. INFO.: US 1999-161820P P 19991027
OTHER SOURCE(S): MARPAT 139:95491
GI



I

AB The present invention provides compds. and methods that are useful for promoting the proliferation of hemopoietic progenitor cells without cell differentiation. Accordingly, the invention provides a compound of formula I wherein: A is -N= or -C(H)=; D is -C(H)=; R1 is hydrogen, amino, azido, or halo; and each R2 is independently hydrogen, or a suitable photolabile caging group; or a salt or a detectably labeled derivative thereof. Certain compds. of formula I (e.g. compds. wherein R1 is hydrogen) may be particularly useful to mobilize intracellular calcium. Other compds. of the invention (e.g. compds. wherein R1 is amino, azido or halo) may be particularly as stable antagonists of **cADPR** (cyclic-ADP-ribose) and **cADPR** induced calcium release. The invention also provides a method to promote the proliferation of a lymphocyte and to enhance the immune system of a mammal comprising **administering** to a mammal in need of such treatment, an amount of a compound of formula I or a salt thereof.

REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1997:134061 CAPLUS

DOCUMENT NUMBER: 126:246347

TITLE: 7-Deaza cyclic adenosine 5'-diphosphate ribose: first example of a Ca2+-mobilizing partial agonist related to cyclic adenosine 5'-diphosphate ribose

AUTHOR(S): Bailey, Victoria C.; Sethi, Jawsinder K.; Fortt, Simon M.; Galione, Antony; Potter, Barry V. L.

CORPORATE SOURCE: Dep. Med. Chem., Univ. Bath, Bath, BA2 7AY, UK

SOURCE: Chemistry & Biology (1997), 4(1), 51-61
CODEN: CBOLE2; ISSN: 1074-5521

PUBLISHER: Current Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Cyclic ADP ribose (**cADPR**), a naturally occurring metabolite of NAD (NAD+), mobilizes Ca2+ from non-mitochondrial stores in a variety of mammalian and invertebrate tissues. It has been shown that **cADPR** activates ryanodine-sensitive Ca2+-release channels, working independently of inositol 1,4,5-trisphosphate (IP3) to mobilize intracellular Ca2+ stores. In some systems, **cADPR** has been shown to be more potent than IP3. The chemo-enzymic synthesis of structurally modified analogs of **cADPR** can provide pharmacol. tools for probing this new Ca2+-signaling pathway. In this work, the authors describe the synthesis and evaluation of a structural mimic of **cADPR** with different Ca2+-releasing properties. 7-Deaza cyclic ADP ribose (7-deaza **cADPR**), a novel **cADPR** analog modified in the purine ring, was synthesized and its ability to release Ca2+ from non-mitochondrial pools in homogenates made from sea urchin eggs was investigated. 7-Deaza **cADPR** was more effective in releasing

Ca2+ than **cADPR**, but it only released approx. 66% of the Ca2+ released by a maximal concentration of **cADPR**. It was also more resistant to hydrolysis than **cADPR**. If the authors **administered** increasing concns. of 7-deaza **cADPR** at the same time as a maximal concentration of **cADPR**, the induction of Ca2+ release by **cADPR** was antagonized. 7-Deaza **cADPR** has a Ca2+-release profile consistent with that of a partial agonist, and it is the first reported example of such a compound to act at the **cADPR** receptor. The imidazole ring of **cADPR** is clearly important in stimulating the Ca2+-release machinery, and the present results demonstrate that structural modification of a site other than position 8 of the purine ring can affect the efficacy of Ca2+ release. 7-Deaza **cADPR** represents a significant step forwards in designing modulators of the **cADPR** signaling pathway.

L20 ANSWER 4 OF 4 MEDLINE on STN
ACCESSION NUMBER: 97223785 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9070427
TITLE: 7-Deaza cyclic adenosine 5'-diphosphate ribose: first example of a Ca(2+)-mobilizing partial agonist related to cyclic adenosine 5'-diphosphate ribose.
AUTHOR: Bailey V C; Sethi J K; Fortt S M; Galione A; Potter B V
CORPORATE SOURCE: Department of Medicinal Chemistry, School of Pharmacy and Pharmacology, University of Bath, UK.
SOURCE: Chemistry & biology, (1997 Jan) Vol. 4, No. 1, pp. 51-61. Journal code: 9500160. ISSN: 1074-5521.
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DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
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AB BACKGROUND: Cyclic adenosine 5'-diphosphate ribose (**cADPR**), a naturally occurring metabolite of nicotinamide adenine dinucleotide (NAD+), mobilizes Ca2+ from non-mitochondrial stores in a variety of mammalian and invertebrate tissues. It has been shown that **cADPR** activates ryanodine-sensitive Ca(2+)-release channels, working independently of inositol 1,4,5-trisphosphate (IP3) to mobilize intracellular Ca2+ stores. In some systems, **cADPR** has been shown to be more potent than IP3. The chemo-enzymatic synthesis of structurally modified analogues of **cADPR** can provide pharmacological tools for probing this new Ca(2+)-signaling pathway. In this work, we describe the synthesis and evaluation of a structural mimic of **cADPR** with different Ca(2+)-releasing properties. RESULTS: 7-Deaza cyclic adenosine 5'-diphosphate ribose (7-deaza **cADPR**), a novel **cADPR** analogue modified in the purine ring, was synthesized and its ability to release Ca2+ from non-mitochondrial pools in homogenates made from sea urchin eggs was investigated. 7-Deaza **cADPR** was more effective in releasing Ca2+ than **cADPR**, but it only released approximately 66% of the Ca2+ released by a maximal concentration of **cADPR**. It was also more resistant to hydrolysis than **cADPR**. If we **administered** increasing concentrations of 7-deaza **cADPR** at the same time as a maximal concentration of **cADPR**, the induction of Ca2+ release by **cADPR** was antagonized. CONCLUSIONS: 7-Deaza **cADPR** has a Ca(2+)-release profile consistent with that of a partial agonist, and it is the first reported example of such a compound to act at the **cADPR** receptor. The imidazole ring of **cADPR** is clearly important in stimulating the Ca(2+)-release machinery, and the present results demonstrate that structural modification of a site other than position 8 of the purine ring can affect the efficacy of Ca2+ release. 7-Deaza **cADPR** represents a significant step forwards in

designing modulators of the **cADPR** signaling pathway.

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=> d his

     (FILE 'HOME' ENTERED AT 11:11:06 ON 06 JUN 2006)

     FILE 'CAPLUS, MEDLINE' ENTERED AT 11:11:17 ON 06 JUN 2006
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L2            22 S INFLAMMAT? (P) CADPR
L3             1 S ENDOTOXEMIA? (P) CADPR
L4            12 S ASTHMA? (P) CADPR
L5             1 S SEPSIS? (P) CADPR
L6             1 S HEMORR? (P) CADPR
L7             1 S SHOCK? (P) CADPR
L8             1 S PANCREATITIS (P) CADPR
L9             1 S CROHN? (P) CADPR
L10            1 S ULCER? (P) CADPR
L11          102 S ADP (P) PHOSPHOROTHIOATE
L12            0 S CADPR (P) PHOSPHOROTHIOATE
L13            0 S CADP (P) PHOSPHOROTHIOATE
L14            0 S CADPR (P) PHOSPHOROTHIOATE
L15            0 S CADPR (P) PHOSPHOROAMIDATE
L16          149 S CADPR (P) ANALOG?
L17            4 S CADPR (P) ANALOG? (P) DISEASE?
L18           16 S CADPR (P) ANALOG? (P) CONDITION?
L19           18 S CADPR (P) PATIENT?
L20            4 S CADPR (P) ADMINISTER?
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